Suid-Afrikaanse Tydskrif vir Geneeskunde : South African Medical Journal

Kaapstad, 9 Januarie 1960 Deel 34 No. 2 Volume 34 Cape Town, 9 January 1960

CAPILLARIA HEPATICA IN MAN — FOLLOW-UP OF A CASE

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In July 1957 there was published in this *Journal*[1] the case history of a young girl (F.G.) affected by *Capillaria hepatica* infestation. The case was the fifth to be reported in world literature, and the first to be recorded in South Africa.

The diagnosis (suggested by Dr. L. Sagorin, of Durban) was made by liver biopsy. Only 2 of the other 4 known cases at that time had been diagnosed in life, and both had died, the one in 4 weeks and the other in 2 years, of fibrosis of the liver. A follow-up of our case F.G. was promised.

Once the diagnosis had been established in the patient F.G., the problem of therapy arose. In searching for a 'specific' form of treatment which might benefit her, we reviewed the previous cases. As they had all ended fatally, we felt that the drugs used in them could be regarded as

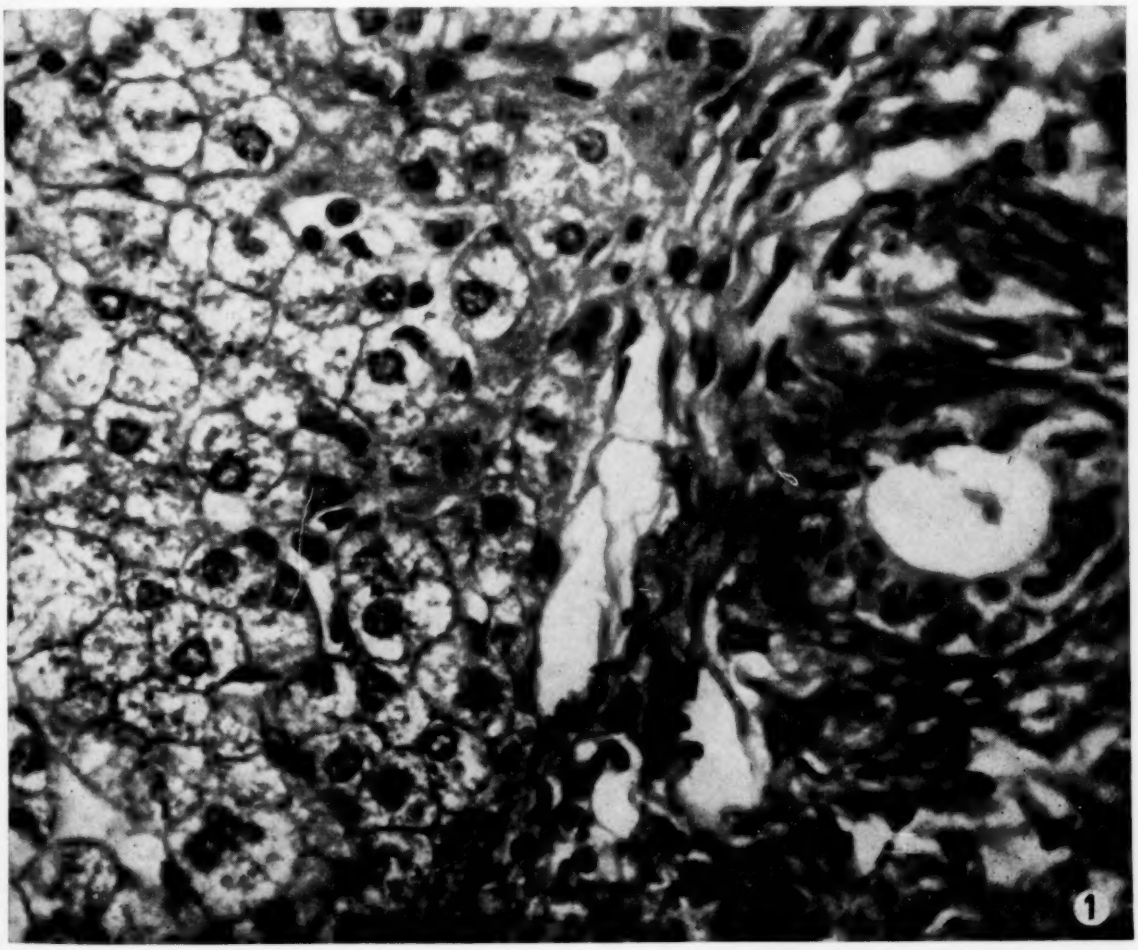

Fig. 1. Patient F.G., February 1959. Liver biopsy showing recovered and normal cytology. The ova have apparently all disappeared, for none were seen on serial section of the biopsy.

ineffective against *Capillaria hepatica* and in this way chloroquine, emetine and hetrazan were excluded. Long courses of antibiotics had already been given to F.G. without obvious lessening of the primary signs of pyrexia and eosinophilia. Antibiotics could therefore also be excluded, except as ancilliary therapy.

Because of certain similarities in the clinical and histological picture of our case to visceral bilharziasis—the eosinophilia, the fibrosis about the ova—it was decided to use antimony in a direct effort against the parasite. The child was extremely ill, with swinging pyrexia, and emaciated to a degree. The apparently least toxic of the antimony preparations was therefore sought and triostam (sodium antimonyl gluconate) decided upon. This preparation had been reported[2-4] as being effective against *Schistosoma haematobium* and *S. mansoni* and the trypanosomes, but we could find no record of its use against trichinella.

The recommended total dosage of triostam for schistosomiasis is from 15 to 20 mg. per kg. body-weight. As the expected weight of a girl of 18 months is 10 kg., the dosage to be given in bilharzia would be 200 mg. In view of the relatively greater toxicity of *Capillaria hepatica* and the risk of fatal outcome if the treatment was not effective it was decided to double this total quantity, and eventually a total of 380 mg. was given intravenously in 7 daily injections, beginning with a pilot dose of 20 mg. in 0·55 c.c. of solution and continued with 6 injections of 60 mg. in 1 c.c. of solution. No reaction was noted of nausea, vomiting or urticarial rash.

Fig. 2. Same patient (F.G.), July 1956. Periportal lesions contain numerous ova of *Capillaria hepatica*. A severe chronic inflammatory lesion with fibrosis encloses the granuloma.

As reported in our earlier paper, the child 10 months after the course was very well indeed. It appeared that our attempt at 'specific' therapy with antimony had succeeded. The patient reported by Otto *et al.*[5] had, however, remained in good condition for 2 years before dying of cirrhosis. It was decided therefore to make no claims until a further liver biopsy could be obtained. We were fortunate in having most cooperative parents, and the child was submitted to a second laparotomy for inspection and biopsy of the liver on 11 February 1959. This was again performed by Mr. J. G. O. Hamman, of Vanderbijlpark, to whom our thanks are due, and revealed a liver of normal size and with a normal surface. None of the yellow-grey nodules noted at the previous exploration were present, and no fibrosis was seen. A section of the liver was taken and submitted for histology. The report (Dr. W. G. Wilcocks), dated 19 February 1959, was as follows: 'Sections of this liver biopsy show the presence of some periportal fibrosis, though this is not very marked. No other significant pathological changes have been observed in the sections examined.' Fig. 1 is a photomicrograph of the biopsy (February 1959), and may be compared with Figs. 3 and 4 of the first article on the case,[1] which were photomicrographs of the biopsy taken in July 1956. Fig 3 of the first article is here reproduced (Fig. 2).

The child, now 4 years and 10 months old, is in excellent health. She is of normal height and weight for her age, bright and active, and shows no signs on clinical examination of the severe illness through which she passed 3½ years ago.

It will be recalled that the full syndrome of *Capillaria hepatica* infection in man includes eosinophilia and hyperglobulinaemia. A comparison of the blood findings at the height of the illness and at the present time is as follows:

	1956	1959
Cephalin cholesterol ..	Positive	Slight flocculation after 48 hours
Thymol turbidity ..	20 units	5 units
Thymol flocculation ..	Positive+++	Negative
Takata Ara	Positive	Negative
Gamma globulin ..	4·4 g.%	0·9 g.%
Eosinophilia	78%	4%

SUMMARY

A follow-up on a case of *Capillaria hepatica* infestation in man is presented 3½ years after treatment.

The child is now in excellent health.

The liver is normal macroscopically, with minimal periportal fibrosis on microscopy.

The blood findings are normal.

Of the 5 cases recorded in world literature up to 1958, our patient alone has survived.

It appears that the use of antimony as a 'specific' form of therapy has been successful.

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FIRST EXPERIENCES WITH A NEW ANTI-HYPERTENSIVE AGENT 'DARENTHIN'

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That the long-term management of severe hypertension is far from satisfactory will be abundantly clear to most practitioners. The indications for treatment, as well as the lack of unanimity which exists, are put forth succintly in a recent masterly review of the subject by Turner.[1,2]

With the advent of the ganglion-blocking agents it appeared that 'medical sympathectomy' had become possible. Experience soon showed, however, that in the majority of cases the treatment was worse than the disease, and patients preferred to suffer the relatively minor symptoms of their disorder rather than the persistent agony of the toxic effects of drugs (dry mouth, severe constipation, visual disturbances, difficulty in urinating, impotence, lassitude, etc.).

In the United States of America there was a swing away from ganglion blockade towards older drugs such as hydrallazine and veratrum, and surgical sympathectomy remained in favour.

A new impetus has been given to therapy with the advent of chlorothiazide and its derivatives, combined with previously used drugs. This served not only to increase the anti-hypertensive effects, but also to increase the cost of treatment and to add new side-effects.

Shortly after the publication of a promising report by Boura *et al.*,[3] the manufacturers of Darenthin were kind enough to let me have a trial supply.

Darenthin (bretylium tosylate), briefly, is a drug which accumulates selectively in the sympathetic ganglia, postganglionic sympathetic fibres and, in general, in those organs with a rich adrenergic innervation, thereby decreasing vascular tone. This effect may be reversed by the administration of adrenergic substances. It appears that only the noradrenaline produced locally at nerve endings is inhibited.

THE TRIAL

So far 7 patients have received the drug for periods varying from 21 to 70 days. The conditions of the trial were uncontrolled, and are just those which obtain in everyday practice. No patient was given bed rest, and everyone went about his usual occupation. Blood pressures in all instances had been recorded many times before treatment began, and were checked daily after its commencement, usually about 2 hours after a dose of the drug had been taken. Pressures were recorded after the patient had been standing for *at least* 2 minutes. Due to the mode of action of Darenthin, there is no point in recording a recumbent blood pressure as it will necessarily be in the pre-treatment region.

Case 1

Miss W., aged 14, has chronic glomerulonephritis with albuminuria, fundal exudates, left ventricular hypertrophy and a blood pressure of 200/130 mm. Hg (fixed). The blood urea was 28 mg.%, maximum urinary concentration 1,020 and the excretion on intravenous pyelography was good. She was given reserpine and ganglion blockade with a drop in the standing blood pressure to 155/100 mm. Hg, but she complained of visual difficulty and nausea. On 5 October 1959, Darenthin was commenced, using 600 mg. daily. A week later the blood pressure was 130/85, and again a week later 150/105 mm. Hg. The dose was increased to 1 g. daily without affecting the blood pressure significantly, but no side-effects were noted.

Case 2

Mr. J., aged 46, suffers from malignant hypertension as evidenced by gross albuminuria, marked left ventricular hypertrophy with a strain pattern on the ECG, visual symptoms and a small patch of exudate in one fundus.

The pre-treatment blood pressure was about 240/150 mm. Hg and a good response could be obtained with reserpine, a ganglion blocker, and chlorothiazide. He felt, however, that life under these conditions was not worth living and ultimately stopped treatment of his own accord and consulted a naturopath. He returned to me feeling very well indeed, but his blood pressure was 240/160 mm. Hg. Darenthin was administered, starting on 600 mg. daily. He complained of some looseness of the bowels and transient stuffiness of the nose as well as tiredness. Daily blood pressure recordings were as follows: 190/140, 160/130, 140/110 mm. Hg. The dose was increased to a maximum of 2 g. daily, at which stage he fainted one morning. A reduction to 1,600 mg. daily has given reasonable control between 120/90 and 130/95 mm. Hg. This patient complained so much of lethargy that the drug was stopped for 3 days, after which he said he felt well, but the blood pressure had risen to 190/150 mm. Hg. Treatment is being recommenced.

Case 3

Mrs. S., aged 55, hypertensive for 6 years at least, had received all the usual forms of therapy with unpleasant side-effects and discontinued all treatment a week before the consultation. Her blood pressure at rest was 200/130 mm. Hg; an auricular gallop was present, and arteriovenous nicking in the optic fundi, as well as spasm and irregularity of the vessels. ECG within normal limits, urine free of albumin and sugar. Noteworthy was the fact that two sisters died of the sequelae of hypertension, and one sister, alive, has hypertensive heart disease.

On 600 mg. of Darenthin daily the blood pressure fell to 115/80, and then rose to 200/130 and 180/120 mm. Hg. The dosage was increased to 1,200 mg. and subsequent pressures have been 130/80, 145/95 and 125/85 mm. Hg. There have been no side-effects.

Case 4

The pre-treatment blood-pressure levels of Mr. B., aged 50, averaged 235/150 mm. Hg. Treatment with other drugs had brought it down to about 185/115 mm. Hg, with slight side-effects from the drugs. He was given Darenthin 100 mg. *t.d.s.*, and on the second day he fainted. About an hour later the systolic blood pressure was 70 mm. Hg. After this he *appeared* to become resistant to the drug, so his doctor built up the dosage to a total of 1,800 mg. daily. At this stage the patient complained of dizziness and said he did not feel well. The reason for this becomes apparent from the following blood pressure readings: Erect, after 3 minutes the blood pressure was 155/110, at 5 minutes 130/100, and at 7 minutes 110/90 mm. Hg. At that time dizziness appeared and no doubt further immobile standing would have produced an even greater fall.

This illustrates one of the difficulties in adjusting the dose, for this patient was being overdosed and casual blood pressure recordings indicated just the opposite.

Case 5

Mrs. C., aged 50. Long-standing malignant hypertension in the region of 250/130 mm. Hg. She responded to ganglion blockers with a pressure of 180/80 mm. Hg, with marked toxic effects. After 10 days on Darenthin, 800 mg. daily, her blood pressure was 200/90 mm. Hg and there were no side-effects. After about 10 days she appeared to become resistant to the drug and the blood pressure rose to 220/130 mm. Hg. The dosage was not increased, and then, as signs of congestive failure appeared, the drug was stopped. The patient had been in failure previously. This case does not represent a fair trial of the drug.

Case 6

Mrs. M., aged 47, had been hypertensive for many years, the blood pressure being in the region of 250/120 mm. Hg. She

had always had tachycardia. She had taken reserpine for 4 years without much effect, and could not tolerate ganglion-blocking agents. This patient's blood pressure, owing to a misunderstanding, had always been measured in the sitting position, averaging 180/100 mm. Hg on 600 mg. of Darenthin daily. Very likely a standing blood pressure would have given lower figures representing adequate control. It is of interest that her tachycardia has disappeared and she reports feeling better than before.

Case 7

A medical practitioner, aged about 45, had been severely hypertensive for many years with an untreated blood-pressure level of 260/160 mm. Hg. His blood urea was 51 mg.%. He had been treating himself with hydrallazine, reserpine, and ganglion-blocking agents, but suffered severe and distressing side-effects.

He commenced taking Darenthin, 600 mg. daily, and the blood pressure came down to 180/110 mm. Hg. The dosage was then gradually increased to a total of 1,600 mg. daily without much improvement. It was therefore lowered again to 600 mg. daily, and dichlorothiazide, one tablet, was taken every alternate day. It has been noted that after taking the dichlorothiazide the blood pressure falls to about 100/70 mm. Hg and then gradually rises over the next 48 hours. This patient is delighted with the results and absence of toxic effects of his new treatment.

DISCUSSION

Darenthin is an effective antihypertensive agent and appears to be free of toxicity. One patient complained of a blocked nose, but this passed off and may not have been due to the drug. A few have noted some tiredness and say they sleep abnormally well. Two patients have had postural faints. In one case the systolic blood pressure an hour later was 70, and in the other case 80 mm. Hg.

The drug acts fully only when patients are in the erect position, partially when sitting, and hardly at all when recumbent. It remains to be seen whether sufficient protection can be given to a hypertensive patient during his standing hours to safeguard him from the effects of the disorder, or whether it will be advisable to use, in combination, some drug which affects the blood pressure in recumbency (probably a drug with a central site of action).

There is no doubt that the advent of bretylium tosylate marks a major advance in the treatment of hypertension, and is the forerunner of further progress.

CONCLUSIONS

1. Seven hypertensive patients have been treated with bretylium tosylate (Darenthin).

2. At one time or another the drug lowered the blood pressure significantly in all cases, even to the point of fainting.

3. Some patients seem to develop a 'resistance' to the drug, but it is felt that this is more apparent than real and is probably due to a faulty technique in recording the blood pressure.

4. Darenthin, in the doses used, is quite free of serious side-effects.

5. Care must be taken, when adjusting the dosage, that the minimum blood pressure reading is obtained, and for this the patient should be allowed to stand for several minutes.

6. It is possible that the addition of small doses of chlorothiazide-like drugs will iron out many of the problems of treatment with Darenthin.

ADDENDUM

Case 1

This patient's blood pressure has remained in the region of 150/100 mm. Hg. No side-effects have occurred and the heavy exudates in the fundi have all but cleared.

Case 2

Much of this patient's symptomatology can be attributed to renal dysfunction, for a recent blood-urea estimation gave a figure of 110 mg.%, with a serum potassium of 3·1 m.Eq./l. After recommencement of treatment, control of the blood pressure has remained very satisfactory, in the region of 130/90 mm./Hg.

Case 3

This patient seems to have developed resistance to the drug. On 1,600 mg. daily, supplemented with a daily dose of 50 mg. of Esidrex, her standing blood pressure remains in the region of 170/110 mm. Hg. Reserpine has been added, and the administration of Esidrex stopped. She insists, however, that she has never felt better and has developed the ability to sleep soundly. This has been mentioned by other patients too.

Case 7

A repeat blood urea on the patient showed a drop from 51 to 43 mg.% since the institution of Darenthin therapy.

Case 8

Since originally writing this paper, one further patient has been on treatment for over 1 month. She is a lady aged 50, who has had marked uncomplicated hypertension for many years, culminating in severe headaches and incapacitating vertigo. Treatment with reserpine, chlorothiazide and a ganglion-blocking agent was given, but the patient felt miserable and was unwilling to cooperate. Her treatment was then changed to Darenthin without supplementary medication and her blood pressure has remained between 130/80 and 150/100 mm. Hg. The pre-treatment level was about 240/150 mm. Hg.

On 1,200 mg. of Darenthin daily her blood pressure fell to 80 systolic and she complained of weakness and dizziness. The dose was therefore reduced to 800 mg. with a resulting slight rise in pressure and abolition of symptoms.

I should like to thank Mr. B. Cuppelditch, of Burroughs Wellcome & Co. (South Africa) Ltd., for generous supplies of Darenthin, and my colleagues for information on patients under their care.

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UNIVERSITEITSNUUS : UNIVERSITY NEWS

UNIVERSITY OF CAPE TOWN

The following postgraduate degrees were conferred at the graduation ceremony held on 10 December 1959:

Doctor of Medicine (Old regulations): L. Vogelpoel, M.B., Ch.B.
Doctor of Medicine: G. S. M. Muller Botha, M.B., Ch.B., Ch.M. (Birm.).
H. de V. Heese, B.Sc. (Stell.), M.B., Ch.B.
P. Lanzkowsky, M.B., Ch.B.
A. S. Truswell, M.B., Ch.B.
Master of Medicine (Anaesthetics): P. J. Horrigan, M. B., Ch.B.
G. J. Roussouw, M.B., Ch.B.
Master of Medicine (Medicine): A. L. Maresky, M.B., Ch.B.
Master of Medicine (Paediatrics): B. L. Goldscmidt, M.B., Ch.B.

VAN DIE REDAKSIE : EDITORIAL

SISTEMIESE LUPUS ERITEMATOSE

Lupus eritematose is reeds in sy plaaslike diskoïede vorm bekend vir nagenoeg honderd-en-twintig jaar. Kaposi het in 1872 daarop gelet dat konstitusionele simptome dikwels daarmee gepaard gaan, maar die beskrywing van 'n niebakteriële endokarditis in twee gevalle met lupus eritematose deur Libman en Sacks in 1924 bevestig die betekenis van 'n verspreide, of sistemiese vorm van lupus eritematose[1] (S.L.E.).

Die term kollageensiekte is in 1942 deur Klemperer, Pollack en Baehr[8] ingevoer *slegs* om daarop te dui dat 'n groep siektes van onbekende etiologie 'n gemeenskaplike patologiese kenmerk het, nl. beskadiging van die intersellulêre stof in bindweefsel, die ‚kollageen'.[1]

Die ontdekking van die ‚L.E.-sel' en ‚-verskynsel' in 1948 deur Hargreaves *et al.*[7] het 'n laboratoriumtoets in die hande van die klinikus geplaas om verdagte gevalle wat diagnostiese probleme het, te help ontdek en sodoende 'n vroeër diagnose te bewerkstellig.

Tot ongeveer 1950 is S.L.E. dus as 'n progressiewe en noodlottige siekte beskou. Jessar *et al.*[2] toon egter in 1953 dat uit 'n betreklike groot reeks, spontane afname van die siekte in ongeveer een derde van die gevalle voorkom.

Dit is bekend dat die steroïede 'n groot invloed op hierdie siektetoestand het, maar 'n noukeurige waardebepaling van die spesifieke indikasies en beperkings van hierdie soort terapie is nog nie bevredigend gelewer nie.[3] Die kwessie van swangerskap en S.L.E. is ook nog nie finaal opgelos nie.[4]

Die etiologie van die siekte is, soos reeds genoem, nog in duisternis gehul. Soos met enige toestand van onbekende etiologie, ontbreek dit ook hier nie aan hipotetiese verklarings nie. Onder die vroegste verklarings is die rol van bakterieë as etiologiese faktor ingesluit, maar hierdie verklaring het gou verdwyn. 'n Hipersensitiwiteitsreaksie skyn tans 'n sterker moontlikheid te wees en wel omdat die serologiese toetse vir sifilis dikwels antikomplimentêr is in hierdie siekte. Die toename van S.L.E. val verder ook saam met die toenemende gebruik van antibiotiese middels, en die L.E.-verskynsel is dan ook al gedemonstreer by persone wat sensitief is vir penisillien. 'n Verhoogde globulien in die serum in hierdie gevalle versterk ook verder die hipersensitiwiteitshipotese.[1] Die beskrywing van twee onlangse gevalle na mesantoïen-terapie is miskien 'n verdere punt ten gunste van dié teorie.[5]

Die fotosensitiwiteit van hierdie pasiënte het 'n moontlike verwantskap met die wanmetabolisme van porfirie ter sprake gebring, maar geen bewyse hiervoor is gevind nie. Endokrien-versteurings is vermoed en 'n abnormale sellulêre metabolisme met verhoogde produksie van gammaglobulien het ook aandag geniet.[1]

In 'n onlangse artikel, wat hopelik die voorloper van ander soortgelyke ondersoeke sal wees, probeer McCombs en Patterson[3] om faktore wat die verloop en prognose van S.L.E. beïnvloed, te ontleed. Uit 'n reeks van sewe-en-sewentig pasiënte vind hulle dat die siekte baie meer seldsaam is by mans as by vrouens, maar dat die mans 'n baie ernstiger beeld vertoon en 'n veel hoër sterftesyfer het. As die diagnose voor een-en-twintig jarige ouderdom gemaak word, is die prognose ernstig, maar diegene by wie die siekte na die ouderdom van vyf-en-veertig jaar ontdek word, het 'n veel gunstiger prognose.[3] Tekens van renale aantasting, selfs by minimale urinêre afwykings, dui op die ernstigste prognose.

Kortikosteroïede terapie verhoed nie die voortskreidende aard van die renale letsel nie, maar het skynbaar tog 'n voorkomende uitwerking. Poliserositis en miokarditis, in die afwesigheid van renale patologie, reageer gunstig op terapie met steroïede.[3]

In sommige gevalle was swangerskap skynbaar 'n presipiterende faktor, maar, as die siekte egter reeds aanwesig is en bewys van renale aantasting afwesig, kan swangerskap met veiligheid onderneem word met 'n redelike verwagting op 'n normale baba.[3]

In die gevalle wat met steroïede behandel is in die genoemde reeks, was die dood te wyte aan nierversaking of die komplikasies van terapie met steroïede in die algemeen.[3]

In 'n siekte wat beslis toeneem, soos blyk uit 'n vergelyking tussen drie twee-jaar periodes (1938 - 1939, 1948 - 1949, en 1954 - 1955) in Swede,[6] behoort ons alle informasie aangaande die etiologie, die natuurlike verloop, en die waarde van steroïede of enige ander vorm van terapie, te verwelkom. Aangesien penisillien, apresolien, en nou ook mesantoïen[5] in sommige gevalle as oorsaaklike faktore voorkom, moet ons verwag om ook nog velerlei ander skadelike middels teen te kom.

'n Toestand wat nie so lank gelede nie nog net as 'n mediese wetenswaardigheid beskou is, het nou 'n belangrike siekte geword, en in die nabye toekoms mag dit selfs 'n baie ernstige probleem word.

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HUMAN CAPILLARIASIS AND ITS TREATMENT

In July 1957 an article by Cochrane, Sagorin and Wilcocks[1] was published in this *Journal* reporting a case of human infection with *Capillaria hepatica* in the person of a White child, fifteen months old when the illness began, living on the small holdings in the outskirts of Vanderbijlpark, Transvaal. Only four human cases had previously been reported in the medical literature, and this was the first case to be recorded in South Africa. The illness began with pyrexia

in June 1956 and during the following three or four months the child was extremely ill, with a swinging temperature. The outstanding findings were enlargement and other changes in the liver, a high degree of eosinophilia, and maximally positive tests for disordered liver function. The eosinophil count ranged from 6,630 to 32,526 per c.mm. (25 - 78% of the total white cells) and the serum gamma globulin reached 5 g. per cent. Liver biopsy showed large numbers of characteristic ova in the portal tract, surrounded by dense cellular infiltration, which in some areas had been replaced by fibrosis, with marked distortion of the liver pattern and degeneration of liver cells. The general appearance suggested that the ova were those of a species of Trichuris, but on further study they were recognized as of *Capillaria hepatica*. Capillaria belongs to the same family as Trichuris (whipworm), which it closely resembles.

This nematode occurs in many animals, and in South Africa it has been found in rats, mice, rabbits, hares, gerbilles and meerkats. At the Institute for Medical Research, Johannesburg, nineteen out of a random group of forty rats received for examination were found to be infested with Capillaria. Where the human patient was living, rats and mice as well as other animals moved freely, and one field rodent (mastomys) trapped at her home in November 1956 showed extensive infestation with Capillaria.

The ova of *Capillaria hepatica* are not discharged in the faeces, and only escape from the liver of the host on its death, when, in rats, they are released through cannibalism on the part of these rodents. Whether the rat which eats the liver develops the disease, or whether the ova must first pass through this animal to be ingested by another, appears to be uncertain. In any case, the embryonated eggs pass to the caecum and thence to the liver, where the worms mature, lay their eggs, and then die and disintegrate. It is interesting to note that geophagy has been recorded in the few known human cases, and that the child infected at Vanderbijlpark is stated to have been 'a prodigious earth-eater'.

In the treatment of their case our authors were faced with the fact that all the four previous cases reported had ended fatally. They therefore rejected the drugs that had been given in those cases and, influenced by certain clinical and histological resemblances to bilharziasis, they selected an antimony preparation, sodium antimomyl gluconate ('triostam'), which had been reported as effective against the haematobium and mansoni bilharzia and against trypanosomes. Large intravenous doses over seven days appeared to clear up the condition and, in a follow-up article[2] which appears in the present issue, Cochrane and Skinstad report that the child is in excellent health and shows no clinical signs of the severe illness she passed through three years ago. On exploratory laparotomy the liver is of normal size and appearance, and on biopsy the only significant pathological change is some 'not very marked' periportal fibrosis. The liver function tests are in strong contrast with those of 1956, the eosinophils now being four per cent and the gamma globulin 0·9 g. per cent. This is the first recovery amongst the five human cases reported.

It will be noted that this study, which is an important contribution to our knowledge of this rare disease in man, in the fields both of diagnosis and treatment, is based on cooperation between laboratory workers of the South African Institute for Medical Research and the clinicians.

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TREATMENT OF HAEMORRHAGE WITH GANGLION-BLOCKING AGENTS: A PRELIMINARY REPORT*

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The complex of the shock reaction has been likened[1] to a fugue, which consists of 3 parts, viz. the exposition, the response and the counterpoint; the exposition being the noxious stimulus or injury, the response the reaction of the cardiovascular system and the organism as a whole, and the counterpoint the means we adopt in treatment. It is in relation to the counterpoint, or treatment, that I shall confine my remarks.

The thesis of this paper is that, in association with adequate blood replacement, ganglion-blocking agents have a fundamental and vital part to play in the treatment of haemorrhage, especially in the more severe types. This therapy is based on the premise that vasoconstriction is often associated with deleterious and undesirable effects, and if prolonged and unrelieved constitutes a lethal factor in the development of 'irreversibility'. An analysis of vasoconstriction and its effects is therefore necessary.

* Paper presented at a meeting of the Transvaal Sub-group of outh African Society of Anaesthetists (M.A.S.A.), 27 May 1959.

Vasoconstrictor Response

Intense peripheral vasoconstriction is the common denominator in virtually all forms of shock, irrespective of the cause, and constitutes a fundamental bodily response. It is primarily protective in nature, being designed to restrict fluid and blood loss and maintain the blood supply to the brain and myocardium. It also incidentally constitutes an effective barrier to the rapid restoration of the blood volume. A great deal of experimental and clinical work has been done in relation to this subject and can be best considered in two main groups, viz. (1) factors related to vasoconstriction and (2) factors accompanying vasodilatation. It will be shown that the former are associated with undesirable sequelae and the latter with beneficial effects.

There is an accumulation of evidence which suggests that irreversible shock may be due to excessive prolongation of the vasoconstrictor reaction, which after a time becomes self-perpetuating.[2-5] Irreversible shock has been produced by prolonged intravenous injection of noradrenaline in animals which had not suffered fluid or blood loss.[6-8]

Therefore the irreversible phase of haemorrhagic shock is not due to a low blood pressure *per se* but rather to the secondary response to vasoconstriction.[9-11]

That vasoconstriction may be so intense that it actually hinders peripheral blood flow, is demonstrated by Wang *et al.*[12] in some excellent experimental work employing cyanide which, because of its action *via* the chemoreceptors, measures central flow, and fluorescin, which measures peripheral flow in that it must leave the peripheral system in order to become visible. These findings have been confirmed by other workers.[6-8]

Zweifach[13] in his classic analysis of the microcirculatory derangements as a basis for the lethal manifestations of experimental shock has elucidated this problem further. He has shown that under conditions of moderate hypotension the operation of homeostatic mechanisms is still adequate to distribute the blood commensurately with the air requirements of tissue metabolism. But when the hypotension is protracted and severe these mechanisms become ineffective, because arterial and venous constriction has now progressed to such an extent that changes distal to the constricted vessels cannot ensure an effective distribution of blood to the tissues through the capillary vessels. Two organs which are especially vulnerable to deficient circulation during haemorrhagic hypotension are the liver and intestine. Zweifach shows quite conclusively how this deficiency of tissue flow involves these organs in the decompensatory trend leading to irreversibility.

Thus it is seen that the vasoconstrictor response, initially protective, if prolonged and severe can become a parent mechanism in the production of irreversibility. Similarly, pain perception is a highly important defence against injury, but no one would suggest that its prolongation was in any way necessary for the survival of the patient. In fact if unrelieved it may cause profound shock and exhaustion. This is an important and basic concept.

Even before vasoconstriction had been observed directly under the microscope, numerous investigators concluded that if the body were freed from the influence of the central nervous system 'marked shock' would fail to produce death in a significant percentage of cases. The influence of the central nervous system has been counteracted by spinal anaesthesia, subarachnoid injection of procaine, transection of the spinal cord, and bilateral thoraco-lumbar sympathectomy.[8,14-16]

It has been demonstrated[17-21] that the protection of experimental animals against the noxious stimuli of vasoconstriction by the pre-shocking administration of blocking agents such as dibenamine, TEA and chlorpromazine results in a significantly higher survival rate in these animals; thus showing that vasoconstriction is not necessarily an effective long-term physiological response to haemorrhage.

Clinically, ganglion-blocking agents were primarily designed to limit bleeding during operation. But it soon became apparent that these agents afforded some protection against the development of shock during elective surgery, and attention immediately became focussed on the possibility that vasomotor activity was the essential cause of peripheral circulatory failure. Johnstone[1] holds that halothane has provided strong, if not conclusive, evidence in favour of the concept that vasoconstriction is an undesirable consequence of trauma or haemorrhage.

Vasopressor Therapy

Despite the foregoing it has been recommended,[22] and is still generally accepted, that all possible attempts should be made to maintain a normotensive head of pressure with vasopressor drugs. This recommendation is deserving of a critical analysis. In spite of the fact that the administration of a vasopressor agent is no guarantee that an adequate blood flow will be maintained in the tissues, a multitude of clinical reports on the use of noradrenaline (norepinephrine in American literature) have appeared. Very few experimental reports, however, can be found on this subject, and those that are available reject this as a rational form of therapy, viz.:

(*a*) Remington *et al.*[17] showed that noradrenaline decreased the survival rate in dogs subjected to haemorrhage.

(*b*) Foster et *al.*[23] working on renal blood flow in haemorrhagic shock, found that in spite of a normal pressure being maintained by noradrenaline 8 out of 10 dogs developed irreversible shock.

(*c*) Wiggers *et al.*[18] showed that the use of a vasopressor might transform 'impending' into 'irreversible' shock.

Why then has noradrenaline been used? It is because we have been led to believe that the irreversible phase of shock is myocardial in nature; since then, the primary and potent action of noradrenaline is believed to be on the contractibility of the myocardium, it is the drug of choice.[24] There are two objections to this, viz.:

1. Adrenaline does not increase the coronary flow and in moderate doses will decrease the flow.

2. All irreversible shock is not myocardial in nature, especially haemorrhagic hypotension, which is the variety under discussion.

How, then, can satisfactory results be obtained if we increase the work load of the heart without increasing (we may even decrease) the coronary arterial flow? The uniformly poor results of noradrenaline in controlled series do not seem to warrant the routine use of the drug in haemorrhagic hypotension.

Mural Tension and Blood Pressure

Two other facts warrant consideration, one a mechanical force and the other related to blood-pressure estimations. Burton[25] has shown that with reduction in the diameter of blood vessels the chances of closure of the lumen secondary to 'tensions forces' in the walls are greatly increased. This postulate is in accordance with the Laplace theory of the 'paradox of the elastic cylinder'. This state of affairs would not apply if vasoconstriction, i.e. the active 'tensions force', is prevented.

There are limitations to the accuracy of baumanometer estimations of blood pressure. Sharpey-Schafer[26] has pointed out that thick arms produce false readings and that this method breaks down when the mean and pulse pressures are low or the peripheral vessels are so constricted as to damp out the small pulsations needed to detect systolic level. Boba and Converse have noted that the blood pressure as measured by an intra-arterial cannula is not an index of capillary circulation. Clinical observation and experimental evidence tend to prove that tissue flow and arterial pressure cannot be directly correlated, and in fact may be completely divorced from each other. Their statement that 'meticulous and assiduous regular estimation of blood pressure is probably more for the therapy of the doctor in attendance than

for the patient' highlights this long and deep-rooted fallacy of the importance of maintaining the blood pressure at all costs.

Philosophy of Therapy

If one can conceive that an acute, severe haemorrhagic episode is an experience that the body was not designed to withstand for any length of time, then one may accept the principle that our therapeutic efforts need not mimic normal physiological responses. In a sense, we should not strive for 'fitness' of the individual in order to observe Cannon's 'fight or flight' theme, but rather for preservation of viability of tissues and organs. Viability does not of necessity imply function. This point has been carried to an extreme in hypothermic anaesthesia, where all bodily functions, including cardiac activity, are suppressed so that the body can withstand insults which are considerably beyond its normal limits of tolerance.

The Essential Problem in Treatment

In a final analysis, therefore, the survival of the organism depends upon the supply of oxygen and nutritive materials to the tissues. This is facilitated by an adequate blood flow to the tissues, which is in essence the prime purpose for which the cardiovascular system was designed. With loss of blood the peripheral flow in many regions is reduced below the point where oxidative tissue metabolism can be effectively carried out. This reduction in flow is due to a widespread peripheral vasoconstriction compensating for the inability of the heart to maintain an effective cardiac output and blood pressure. The net result is a compensatory situation in which blood pressure is maintained at the expense of blood flow to the tissues. In this situation the relative autonomy of the terminal vascular bed becomes the dominant factor and gives rise to changes antagonistic to the initial compensatory readjustment. The longer this stage of the syndrome is allowed to progress the more refractory to fluid replacement the body becomes, and fatal circulatory collapse ensues. This imbalance of blood loss and the vasoconstrictor response is contained in Boba and Converse's apt definition of shock, viz., 'The sympathetic response to an acute reduction in cardiac output (primary or secondary) wherein the response becomes an independent noxious stimulus'. There are thus two major problems in therapy, viz.:

1. To combat the decrease in cardiac output.
2. To prevent damage from the prolonged overwhelming sympathetic vasoconstrictor response.

With haemorrhage the decrease in cardiac output is secondary to a decrease in venous return, and is treated by blood replacement.

The rational approach to the treatment of the vasoconstrictor response is fairly obvious. Firstly, it is important to interrupt the train of events progressing to irreversibility. Secondly it is desirable that the barrier against rapid blood replacement which vasoconstriction causes should be removed. Finally, the blood that is transfused should be able to reach the tissues. In other words, not only is it important to restore blood volume, but we must ensure that the blood is able to subserve its vital function of maintaining cellular integrity and viability.

Administration of a ganglion-blocking agent, by virtue of its vasodilator effect, will satisfy the above criteriae.

Ganglioplegic Effects on Special Organs

The use of deliberate hypotension in anaesthesia has stimulated a number of investigations in the field of circulation at low pressures, which serve to indicate that some of our commonly accepted concepts need re-evaluation.

In the kidney after injection of a ganglion-blocking agent very little change in renal blood flow can be observed. If the blood pressure is then raised with a sympathomimetic amine a sharp fall in renal blood flow co-existent with an increase in systolic blood pressure can be demonstrated.[23,27] Even at extremely low heads of systemic blood pressure, urinary output is maintained, though somewhat depressed.[28]

In the brain the circulation may be 'pressure regulated', or at least the calibre of an artery may be a pure function of the head of pressure to which it is exposed.[29,30] With low arterial pressures (regardless of how achieved) cerebral vasodilation is the response. With high arterial pressures vasoconstriction is the response. The vessels of the brain are apparently designed to regulate the resistance to flow in their own circulatory area. Kety *et al.*[31] defined the term 'cerebrovascular resistance', and showed that its value varies in the same direction as the arterial blood pressure. This in no way contradicts the fact that anoxia is a powerful stimulus to cerebral vasodilation. Philosophically, the cerebrovascular response to anoxia supports the concept that vasodilation affords better circulation.

As regards the heart, there are two factors operating from the administration of a ganglion-blocking agent, viz. (1) a reduction in the work of the heart as a consequence of decreased peripheral resistance, and (2) a reduction in coronary arterial flow. Hackel *et al.*[32] and Eckenhoff *et al.*,[33] working under experimental conditions, have reached the conclusion that with reduced peripheral resistance the reduction in cardiac work is relatively greater than the reduction in coronary flow.

Capillary Reinfusion or Auto-infusion

It is important to reiterate that ganglion-blocking agents should not be exhibited unless there is adequate blood available for concomitant transfusion. The quantity of blood replaced calls for comment, and Ruscoe Clark's[34] contention that what is required is 'bigger and better' transfusions needs some modification, based on the phenomenon of capillary reinfusion, sometimes labelled auto-infusion.

The reinfusion which occurs immediately after haemorrhagic shock has been observed directly by determinations of the total blood volume before and after haemorrhage,[35] and indirectly by observing the cardiovascular response to the quick reinjection of all shed blood.[20] It has also been shown that rapid transfusion of volumes equal to those removed from experimentally bled animals has produced primary cardiac failure because the post-transfusion blood volume exceeds the volume before haemorrhage.[36,37] This is responsible for the theory of partial replacement therapy which is discussed below.

If the source of the additional fluid is the extravascular space, and if the shift occurs at the capillary bed, certain corollaries should follow:

(*a*) The amount of blood that can be shed with one maximal bleeding must be unpredictable because it is related to the functional status of the animal, including fluid reserves and the ability to mobilize these reserves. This has been demonstrated experimentally.[35,36]

(*b*) If the source of the fluid is the extravascular compartment and if this reservoir is not replenished, a succeeding lethal haemorrhage should not yield as much blood as it would under normal conditions. Foreman[37] has shown that the bleeding volume of dogs subjected to a shocking procedure 1 hour before the lethal haemorrhage was consistently lower than the bleeding volume in a series of normal control dogs.

Because the extravascular fluid spaces must supply a reservoir of fluid for withdrawal into the intravascular compartment the use of intravenous glucose in water or normal saline to replace this reservoir is of some importance.

With intense precapillary vasoconstriction the hydrostatic pressure of the capillary will drop, and a level will be reached where the osmotic pressure of the plasma is higher than that of the hydrostatic pressure, and thus the flow of fluid will be reversed and pass into the intravascular compartment. It has been stated that the beneficial effects of the ganglion-blocking agents are due to the fact, that by preventing vasoconstriction, a greater surface for reinfusion is afforded.[18]

CASES TREATED

Six cases, 3 treated with chlorpromazine and 3 with arfonad, will now be described. This series is very small, which is due to the fact that only cases that were severely shocked and might have succumbed to conventional therapy were treated—in an endeavour to assess the merit of the clinical applications of this concept and not to be lulled into a false sense of security and success by treating milder cases that would have responded to simpler means.

Most of the published work on the use of ganglion-blocking agents has been done in experimental animals, and very little in human beings.

Chlorpromazine

Case 1

A 20-year-old Bantu male, admitted comatose, pulseless and with cold extremities, Cheyne-Stokes breathing, and blood pressure 80/0 mm. Hg. Bright red blood was catheterized and there was marked bruising over the right loin. A diagnosis of ruptured kidney was made; in addition displaced fragments of the pelvis could be felt *per rectum*.

Blood transfusion was immediately commenced and 12·5 mg. of chlorpromazine was given intravenously 35 minutes after admission. A noticeable effect following the chlorpromazine was the greater speed with which the blood could be administered. The extremities became warmer and the blood pressure rose to 90/25. In 2 hours 6 pints of blood, 1 pint of dextran, 1 pint of plasma and 1 litre of dextrose-saline was given. The patient, however, never recovered consciousness, and he died on the way to the operating theatre.

Case 2

An obese 65-year-old Malay female, admitted with a 14-hour history. She was grey, exhibited marked pallor, and had cold extremities and a very thready pulse. The abdomen was distended and rigid, and X-ray revealed the presence of gas under both sides of the diaphragm. ECG showed evidence of a posterolateral cardiac infarct, probably not of recent origin. In spite of the indications for surgery she was not considered a good candidate, because the exact diagnosis was in doubt.

Blood and plasma were administered and also 25 mg. of chlorpromazine intravenously. An apparent improvement was noted in that the extremities became warmer and pink. Laparotomy was performed 3 hours later, when a duodenal perforation was sutured and 5 stones removed from the gall-bladder. The patient made an uneventful recovery and was discharged 10 days later.

Case 3

A Bantu male aged 22 years, assaulted. Examination revealed multiple stab wounds as well as a large left haemothorax with mediastinal shift. The patient was pulseless and cold and had no recordable blood pressure. Blood transfusion was commenced and he responded; but 1 hour after admission he collapsed, and the wound in his chest began to expand with blood. Largactil 25 mg. intravenously, was given at this point, and the chest wound was opened in the ward, clot evacuated, and a bleeding intercostal vessel clamped and ligated. He was given further transfusion and made a good recovery.

Chlorpromazine has shown to have beneficial effects as a pre-shocking procedure.[21] This is borne out by the response in case 2 and to some extent in case 3. Case 1, being an already established case of shock did not respond, which supports the conclusion from the experimental work of Hershey *et al.*[21] that the administration of chlorpromazine after the onset of haemorrhage does not afford protection. Furthermore, chlorpromazine has various mechanisms of action and has the undesirable effect of increasing the pulse rate.

Arfonad

Arfonad (d-3,4 (1′, 3′-dibenzyl-2′-ketonim-idazolido-1,2-trimethylene thiophanium d-camphor sulphonate) is a thiophanium derivative which has the characteristic ganglionic blocking and hypotensive effect of tetra-ethyl-ammonium bromide (TEA),[38] and its main action in man is assumed to be primarily ganglionic blockade. Sarnoff *et al.*[41] state that the continuous graded intravenous administration of arfonad appears to 'provide a quantitative method of diminishing peripheral vascular resistance, in a gentler and more promptly controllable manner than has been possible by other means', and they suggested its use in the treatment of pulmonary oedema. Arfonad has assumed an increasingly important place in the production of deliberate hypotension during surgery.[40-43]

Arfonad was first used in the treatment of haemorrhagic shock by Converse *et al.*[39,44] They treated 8 cases with 'heartening' success in 25%. In all cases the haemorrhage occurred in the operating theatre. This had the advantage that the blood loss could be accurately estimated, and also that therapy could be undertaken relatively early. The 3 cases treated in the present series are as follows:

Case 1

A Bantu male aged 56 years, who had undergone 5 operations for tuberculous peritonitis and adhesions with obstruction. He was still left with a faecal fistula of the small bowel, and a distal block in the caecal area. Laparotomy was undertaken, the fistula closed, and a right hemicolectomy performed.

He recovered from the anaesthetic and was returned to the ward. One hour later he suddenly deteriorated. He was now cold, pulseless and cyanotic, with no recordable blood pressure. In addition his dressings were soaked with blood and, on removal of these, blood was found to be gushing out of his drainage tube.

He was immediately taken to the theatre, where blood transfusion was commenced and arfonad administered at the same time as a 0·1% solution in normal saline. The response was satisfactory in that the patient became warm and pink and the bleeding did not increase. The abdomen was reopened and unfortunately no single bleeder was found. Instead a widespread and diffuse ooze was present, which it was impossible to control, despite adequate blood replacement. The abdomen was packed, but the patient died, and the cause of death was thought to be a disorder of coagulation.

Case 2

A Bantu female 49 years old, admitted with a history of having been kicked in the abdomen 20 hours before admission. On examination the abdomen was found to be rigid. Laparotomy was performed and gross peritonitis due to a traumatic perforation of the terminal ileum was dealt with. Just as the peritoneum was about to be closed cardiac arrest supervened. A left thoracotomy was immediately performed and cardiac massage instituted. With the return of the cardiac beat arfonad infusion was commenced. The patient recovered and was returned to the ward. She regained consciousness completely and was perfectly rational She still showed signs of toxaemia and 28 hours after operation there was, if anything, some deterioration in her condition. Levophed was then administered. She died 20 minutes later.

Case 3

A female Bantu aged 38 years, admitted to the gynaecological ward. She was suffering from stage-III carcinoma of the cervix, which had been treated with radium 6 weeks before admission. She was extremely pale, with a very thready pulse, dry tongue and shrunken eyes, and extremely restless, and there was profuse bleeding from the vagina. The blood pressure was 50/0 mm. Hg and the haemoglobin 4·5 gm.%.

She was plugged vaginally and 5 pints of blood immediately transfused. As her blood pressure began to rise and as the last pint of blood was running in, another profuse vaginal haemorrhage occurred, with extrusion of the plug. She was now again very pale and pulseless, no blood pressure was obtained, and she was very thirsty and drowsy. Arfonad infusion of 0·1% in normal saline as well as further blood transfusion was commenced. The patient improved and the arfonad was continued over the next 24 hours, a total of 800 mg. being administered. Blood replacement was continued, a further 4 pints being given.

The patient recovered; she was no longer thirsty or restless and her blood pressure rose to 90/60, which she tolerated without any ill effects; the daily output of urine was 700 c.c. The vaginal pack was subsequently removed with no recurrence of bleeding, and she was discharged from hospital without any cerebral complications.

In these cases shock had been present for some time and was very well developed when arfonad was administered. Although 2 out of the 3 patients finally died, they died of other factors and not because of the administration of arfonad.

The survival rate in the 6 cases reported is not statistically significant, but it does appear that a ganglion-blocking agent with the attributes of ready controllability and speed of action is of considerable value in the treatment of haemorrhage.

DISCUSSION

No undue emphasis was placed on blood-pressure estimations, the colour and temperature of the extremities being used as an index of beneficial response. Nor was any attempt made to replace the blood loss volume for volume.

Converse *et al.*[44] have demonstrated, by estimations of blood volume made with radiochromate-51, that induction of hypotension in animals with arfonad results in an auto-infusion of 7-12% of the control volume. Thus, if the small clinical experience here reported, together with the work of Converse *et al.* is integrated with the laboratory experience of others, it would appear that controlled vasodilation produced by drugs takes advantage of the beneficial fraction of the normal response to loss of intravascular fluid, while blocking those responses which in themselves may become pathophysiological stimuli. In other words, part of the normal mechanism for defence against blood loss is maintained, viz. low capillary pressure allowing reinfusion from extravascular fluid spaces to take place, while vasoconstriction with its attendant anoxia is effectively blocked. The previously mentioned concept of maintaining blood flow to all organs—temporarily permitting viability but not function—appears to be satisfied. It must again be stressed that ganglion-blocking agents should on no account be administered without adequate and similtaneous blood replacement.

There must be limits to this method of therapy. It is obviously of some importance to give quantitative expression to these limitations in regard to the parameters of blood volume in which this approach can function. In age groups in which atherosclerosis produces a rigid vascular system, the haemodynamic responses postulated for this mode of treatment probably do not obtain. It also appears to be essential to use gravity as an aid to cerebral blood flow in the presence of very subnormal pressures.

The Physiological Significance of the Autonomic Nervous System

The study of the above-mentioned pathophysiological states, if followed to a logical conclusion, leads to the rather disconcerting conclusion that the autonomic nervous system may be a liability to the body.[2] This trend of thought makes the concept of ganglion blockade in haemorrhage less incongruous than it at first might appear.

The usual teaching about the sympatho-adrenal system is based on Cannon's work[45] and is expressed in the classical statement that it is a system which confers an advantage on the organism when it meets emergency of some sort, resulting in the need for staying to fight, or taking flight, or expressing fright. It is fairly obvious from experimental and clinical evidence that this system is not essential for ordinary life. Cannon himself showed that after the sympathetic nervous system had been ablated a cat could still lead a relatively normal life.

The sympathetic system does not play the vital role in survival of the organism that the adrenals, pituitary, kidneys and liver play. It becomes apparent that however important the autonomic nervous system may have been for some lower organism, it no longer occupies such a key position for mammalian life, or in particular for human life. Indeed, its presence may in fact amount to a liability, in that it makes possible the play of emotion of all sorts on our viscera, and so, perhaps, gives rise to the psychosomatic disorders. It is interesting, philosophically, to balance the physiological loss which would be incurred by abrogating our right to an autonomic nervous system against the clinical gain in the diseases from which we should be freed.

However, Cannon's view was that the sympathetic played its role not in normal life but under emergency conditions. If this were true it would be difficult to see how inactivation of the sympathetic by drugs could favour survival in haemorrhage, tourniquest shock, or poisoning with anticholinesterases. It would also be impossible to accept that the human organism is made ready for elaborate and taxing surgical procedures when all the autonomic defences are shattered by refrigeration and whole batteries of paralytic cocktails.

The impression is thus gained that the autonomic nervous system is an evolutionary heritage which, however useful in our ancestral past, now seems to be out of gear with the requirements of human life, with its continued and varied emotional pressures.

SUMMARY

1. Evidence is submitted of the lethal part that vasoconstriction can play in the development of 'irreversibility'.

2. The deleterious effect, and the irrational basis for the use, of vasopressor therapy is detailed.

3. The beneficial effects of counteracting the vasoconstrictor response by destroying nervous pathways and by means of ganglion-blocking agents is demonstrated.

4. The fallacy of a direct relationship between blood pressure and tissue flow is indicated.

5. The concept of concentrating on viability rather than on function as an initial measure by using ganglion-blocking agents (in addition to blood transfusion) is elaborated.

6. Certain characteristics and effects of these agents are noted.

7. A small series of 6 cases treated is presented.

8. The philosophy that the autonomic nervous system has outgrown its usefulness to man and represents an evolutionary heritage is suggested.

I should like to thank Dr. M. Barlow and Dr. J. Gottlich for their help in treating some of the cases. I am indebted to Prof. D. J. du Plessis and Mr. Boris Lewin for reading the manuscript. To Dr. G. D. Elliott, Superintendent of Coronation Hospital, I am grateful for permission to report on the cases treated.

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CHLORPROPAMIDE* (DIABINESE) IN DIABETES, WITH SPECIAL REFERENCE TO TOLBUTAMIDE-FAILED CASES

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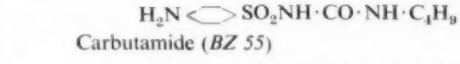
In this age of great therapeutic advances we are witnessing the apparent paradox of pharmacological substances—the sulphonylurea drugs—being used for the correction of a physiological aberration such as diabetes on the one hand, and on the other hand of a physiological agent—cortisone—being used for the treatment or 'cure' of a variety of inflammatory and allergic conditions.

With the discovery of insulin it seemed that the final answer to diabetic treatment was at hand, but as time has gone on it has become clear that insulin is necessary only in a proportion of diabetics. In the acute-onset diabetes of the juvenile type, often associated with ketosis, insulin will largely correct the physiological abnormality. The maturity-onset type of diabetic—who has been shown to have available insulin in his plasma—is not fundamentally benefited, as far as we know, by exogenous insulin.

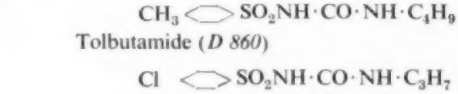
Attempts to correct the hyperglycaemia in diabetes by drugs other than insulin proved unsuccessful or impracticable until the advent of the sulphonylureas. It is problematical whether the other biochemical abnormalities of diabetes mellitus are corrected by these pharmacological agents.

In the treatment of diabetes mellitus our aim should be the search for the biochemical abnormality and its correction. The sulphonylurea drugs may prove to be a stepping stone in this direction.

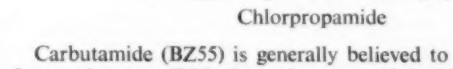
The similarity of the chemical structure of the sulphonylureas is evident from their formulae:



Carbutamide (*BZ 55*)



Tolbutamide (*D 860*)



Chlorpropamide

Carbutamide (BZ55) is generally believed to be too toxic for routine use. With the replacement of the NH_2 group by CH_3 (tolbutamide) the toxic effects were greatly diminished,

* Produced by the Pfizer Laboratories, of America, under the trade name Diabinese. We are indebted to Messrs. Pfizer, of Johannesburg, for initial supplies of this drug.

but unfortunately the hypoglycaemic activity was also somewhat decreased.

Chlorpropamide is the latest addition to these drugs in general use. A chlorine radical has replaced the NH_2 or CH_3 group.

There are many puzzling features connected with the clinical applications of these drugs. If we consider the maturity-onset type of diabetes only—why do some patients in this group respond to the sulphonylureas and others not? A proportion of the diabetics who respond satisfactorily to tolbutamide fail to respond after continued treatment. Why should this secondary failure occur? Why may patients respond to chlorpropamide when tolbutamide has failed either initially or later? Is there a difference in their action (or is the apparent difference merely one of absorption and blood level)?

In this series of cases the clinical effect of chlorpropamide in diabetes mellitus has been studied and special attention has been paid to those cases in which there had been secondary tolbutamide failure.

METHODS AND MATERIAL

The 56 diabetics studied here were seen at the diabetic clinic of Groote Schuur Hospital. Of these, 52 (all but 4) were of the maturity-onset type, all over 40 years of age. Generally they had been seen over a period of years and all but one had been treated with other hypoglycaemic agents previously.

The fluctuations in blood sugar have been observed in some of the cases over a period of years (in a few cases one of us, J.B.H., has observed such fluctuations with remissions and relapses in the diabetic state for over 10 years). This has enabled us to form some idea of comparative response to the various hypoglycaemic agents.

The subjects were asked to report for a fasting blood-sugar estimation (Hagedorn-Jensen method) approximately once a week. In addition many of them kept records of qualitative tests of the urine. Chlorpropamide was given in a dosage of 2 tablets (2×250 mg.) a day. On rare occasions the dose was increased to 3 tablets and sometimes it was reduced to 1 a day.

Where a good hypoglycaemic response had been achieved on chlorpropamide, as indicated by fasting blood-sugar estimations, a glucose tolerance test was done in some cases. Some patients were further examined by an augmented cortisone tolerance test while remaining on chlorpropamide.

A further 4 acute-onset diabetics who were on insulin were also given chlorpropamide to determine whether this would lower the insulin requirement in these cases.

'Excellent' response indicates a reduction of the fasting blood sugar to within the normal range (under 120 mg. per 100 ml.) and virtual absence of glycosuria. 'Poor' indicates no apparent effect. 'Partial' indicates some definite effect of chlorpropamide; although the blood sugar did not become quite normal, control may yet be considered very satisfactory in some of the cases so classified.

RESULTS

Excellent hypoglycaemic response was obtained in 24 of the maturity-onset cases, 'partial' in 17 and 'poor' in 11.

In none of the 4 acute-onset diabetics could the dosage of insulin be lowered whilst on chlorpropamide.

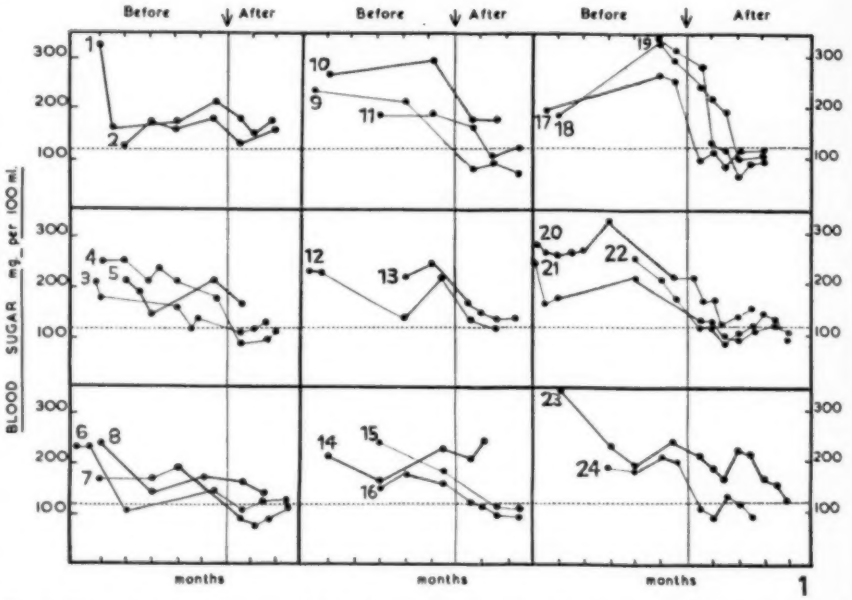


Fig. 1. Chart showing response of first 24 patients treated with chlorpropamide (fasting blood sugars before and after chlorpropamide).

A composite graph (Fig. 1) gives some idea of the response to chlorpropamide in the first 24 patients treated by one of us (J.B.H.).

Relation to previous tolbutamide effect

Of the 52 maturity-onset patients, 51 had previously had tolbutamide and 43 had failed to respond to this drug. In the latter group there were 18 primary tolbutamide failures and 25 secondary failures. The test imposed on chlorpropamide in this particular trial was therefore a very stringent one. An excellent response to chlorpropamide was obtained in 20 of

TABLE I. CHLORPROPAMIDE RESPONSE IN RELATION TO PRIOR EFFECT OF TOLBUTAMIDE

Tolbutamide Status	*Response to Chlorpropamide*		
	Excellent	*Partial*	*Poor*
Primary failure ..	8	6	4
Secondary failure ..	11	8	6
Partial response ..	0	2	0
Maintained control ..	4	1	1
Not used (on insulin)	1	0	0
	24	17	11

the 43 tolbutamide failures, and a partial response in a further 14. (Table I shows a further break-down of the chlorpropamide response in relation to prior tolbutamide effect.)

Relation to race, sex and body build

All the patients were White except 3, who were Cape Coloured. Two of these 3 responded very well to chlorpropamide. There were only 11 males in our series. Less than one-third of our White patients were considered obese—illustrating our belief that obese diabetics should be treated by diet only as far as possible.

Relation to duration of diabetes

Table II indicates that an excellent response is quite likely even where diabetes has been present for over 10 years.

TABLE II. RESPONSE TO CHLORPROPAMIDE IN RELATION TO DURATION OF DIABETES

Duration of Diabetes (years)	*Response to Chlorpropamide*		
	Excellent	*Partial*	*Poor*
Under 10	19	11	7
Over 10	5	6	4

Relation to previous administration of insulin

More than one-third of our patients had previously been taking insulin. Table III makes it clear that there is no

TABLE III. RESPONSE TO CHLORPROPAMIDE IN RELATION TO PREVIOUS USE OF INSULIN

Previous Insulin	*Response to Chlorpropamide*		
	Excellent	*Partial*	*Poor*
Yes	9	8	4
No	15	8	8

apparent difference in response to chlorpropamide in the two groups. One patient, an obese Coloured female of 60, was poorly controlled on 90 units of insulin daily, and completely failed to respond to tolbutamide. Her response to chlorpropamide is classed as excellent.

Toxic effects

Serious toxic effects were not encountered in this series. One male patient, who failed to respond, said that attacks of Menière's vertigo were more frequent when he was taking chlorpropamide. A complaint of 'feeling queer', associated with palpitations, necessitated stopping the drug in 2 cases. Patients with symptoms of gastric intolerance were able to continue taking the drug when magnesium trisilicate powder was prescribed and the dose of the drug reduced. Many of the patients who showed a good hypoglycaemic response also experienced increased well-being.

INDIVIDUAL CASES

A summary of 3 case reports will serve to give more information about the nature of the response in the individual case.

Case 1 (*No.* 19 *in Fig.* 1)

A typical good response was obtained in D.R., a middle-aged European female, whose remissions and relapses in diabetes had been followed over a period of 12 years. Tolbutamide, which had at first produced an excellent result, failed to influence the hyperglycaemia on continued treatment. The administration of 2 tablets of chlorpropamide (0·5 g.) effected a prompt response. A fasting blood sugar of over 300 mg. per 100 ml. was lowered to less than 100 mg. per 100 ml. and 2 weeks after starting chlorpropamide remained at that low level. Urine tested 4 times a day remained sugar free.

Case 2 (*No.* 20 *in Fig.* 1)

E.C. is a middle-aged European female in whom fasting blood-sugar tests over a period of years had always given results between 200 and 300 mg. Before administration of chlorpropamide this patient was on 20 - 30 units of lente insulin and 4 - 6 tablets of tolbutamide a day, with fasting blood-sugar levels remaining consistently between 200 and 300 mg. Chlorpropamide in doses of 2 (later 3) tablets a day for the first time in years brought down the fasting blood sugar to a near-normal level of (140–150 mg.)

Case 3 (*No.* 13 *in Fig.* 1)

R.D., a European male aged 42 years, was seen 2 years previously on a dose of 60 units of insulin daily. He was found to have low fasting blood-sugar levels, the urine being constantly sugar-free. Insulin was slowly reduced and after a while stopped; the fasting blood sugars remained normal for about 2 years, when hyperglycaemia manifested itself. Three tablets of chlorpropamide lowered the fasting blood sugar from 240 mg. to 130 mg. and the patient has remained well on 3 tablets a day. Insulin has not been found necessary

DISCUSSION

In this investigation, chlorpropamide was shown to have a powerful blood-sugar lowering effect. Oral glucose-tolerance tests (using 50 g. of glucose), however, whilst the patients were being treated with chlorpropamide, still showed a considerable hyperglycaemia in the majority of the cases

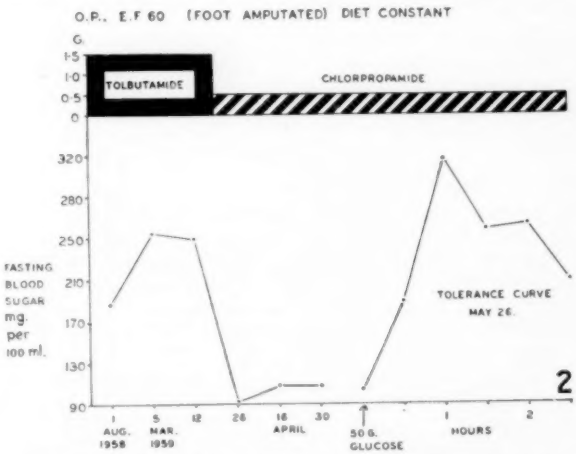


Fig. 2. Case 17 in Fig. 1. Good response to chlorpropamide, but note abnormal glucose tolerance despite low fasting levels.

(e.g. Fig. 2). As found with the earlier sulphonylureas, therefore, the major effect of chlorpropamide is in the basal or fasting blood-sugar level, rather than on the disposal of ingested carbohydrates.

Chlorpropamide was found in this series to be frequently very effective where there was primary or secondary tolbutamide failure (e.g. No. 19 in Fig. 1). In some instances 1 tablet of chlorpropamide (250 mg.) was more effective than 6 tablets of tolbutamide (3 g.). It would appear unlikely then that there is a purely quantitative difference in action of these drugs, but we performed no studies of blood levels.

This series is plainly not large enough to judge the toxicity of the drug, which has been implicated in the appearance of jaundice in certain cases overseas. Its more powerful hypoglycaemic effect may give rise to serious reactions, though we have seen none.

It would appear that chlorpropamide may be effective in maturity-onset diabetes, whatever the age, sex or body build of the patient, whatever the duration of diabetes, whatever response there had been to tolbutamide, and whether or not insulin had been used previously.

Our present practice is to start with tolbutamide (maximum dose 1 g. 3 times a day) where a sulphonylurea appears indicated (i.e. in maturity-onset cases in which diet alone has failed). If the response is not satisfactory, or if secondary failure occurs, a trial of chlorpropamide is made.

SUMMARY

1. The response to chlorpropamide has been assessed in 56 diabetic patients, all but 4 being of maturity-onset type.

2. The drug was satisfactory in a high proportion of cases, and appears to be particularly useful in patients in whom there has been primary or secondary tolbutamide failure.

3. No serious toxic effects were seen in this series.

We should like to thank Prof. J. E. Kench and his assistants for their great help.

The work was financed by the University of Cape Town Staff Research Fund, Messrs. Pfizer, and the South African Council for Scientific and Industrial Research.

CLINICAL TRIAL OF AMINO-METHYLBENZOL-SULPHONYL-CYCLOHEXYLUREA ('METAHEXAMIDE') IN DIABETICS AFTER FAILURE OF TOLBUTAMIDE

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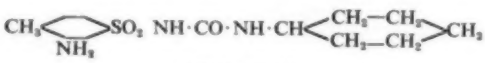
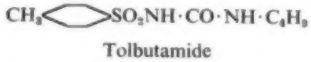
Metahexamide* is a sulphonyl urea derivative, N. 3 amino 4 methylbenzol-sulphonyl-N¹-cyclohexylureum, with a structural formula (compared with tolbutamide) as follows:



Metahexamide



Tolbutamide

Like its analogues, tolbutamide and chlorpropamide, it is capable of lowering the blood sugar in normal subjects and in some diabetics; not in diabetes of the juvenile type. Its breakdown and excretion are slower than with tolbutamide, the blood level being reduced 50% from a maximum in about 20 hours.

Toxic Effects in Man

Occasional allergic skin reactions and gastro-intestinal irritation appeared to be the only effects of metahexamide at first. Unfortunately, while we were in the process of performing a clinical trial of this substance, the makers reported that severe hepatic disturbances had occurred in some patients while taking it, and consequently they very correctly withdrew all supplies.

We report below, briefly and for record purposes, our results until the cessation of the trial.

* The metahexamide and the scientific data thereon were kindly supplied by Messrs. Hoechst Pharmaceuticals of South Africa. Noristan Laboratories (Pretoria) also supplied some tablets, which had not been used by the time the trial was discontinued.

Methods

The patients chosen for the trial had diabetes of maturity-onset type, had never had ketosis and, except one, were all over 40. The duration of their diabetes varied from 1 to 20 years, and just over half had received insulin previously. *All* cases, however, had failed to respond adequately to both diet and tolbutamide, so that this trial aimed at being rather a searching test for metahexamide.

The subjects were out-patients attending a diabetic clinic and seen for the most part weekly. Several fasting blood sugars were estimated in the weeks before metahexamide was started, while the patient was taking no drug or was on tolbutamide only. Urine samples were tested at the clinic and also by the patient at home. In some cases the 24-hour urine sugar was estimated on several occasions. Weekly weight records were kept. As discussed previously,[1] we consider it essential that a period on *no* treatment other than diet should precede the evaluation of an oral drug.

The patients were started on 50 or 100 mg. of metahexamide and this was increased gradually to a maximum of 300 mg., taken in a single daily dose.

Results

Results are classed as 'success' if the blood sugar is brought within normal range (though we realize that carbohydrate tolerance may still be grossly abnormal) and the urine tests showed 'nil' or 'trace'. A 'partial success' indicates a distinct improvement, and 'failure' no apparent effect at all.

The patients receiving the drug numbered 28, and the effects are assessed in 27; one patient had to stop therapy

because of nausea, vomiting and headaches. The make-up of the patients was as follows:

'RACE'		BODY BUILD	
White	20	Slim	10
Coloured (i.e. half-caste) ..	7	Medium ..	15
		Fat	2
	27		27

PRIOR RESPONSE TO TOLBUTAMIDE

Primary failure	13
Secondary failure, following initial success	11
Partial success	3
	27

The response to metahexamide was classed as follows:

Success	3
Partial success	6
Failure	18
	27

The 3 'successes' were aged 32, 65 and 71; none was obese; the 2 older patients had never had insulin. The response of the younger patient is shown in Fig. 1.

The response to metahexamide bore no relation to the tolbutamide response; for instance, 1 'success' and 3 'partial successes' had been primary tolbutamide failures.

No obvious trend in total white-cell count or serum-cholesterol level was evident from metahexamide therapy. The serum cholesterol in one patient, however, who responded successfully to metahexamide, dropped from 237 mg. per 100 ml. to 179 in 10 weeks (Fig. 1). These were the only levels obtained in that patient.

Comment

Body build. It is noteworthy that on analysis of our figures we found not a single over-weight patient in the White racial group who received metahexamide, although the patients in the trial were quite unselected, apart from being tolbutamide failures and able to attend regularly. This indicates our reluctance to use the sulphonyl-ureas in obese subjects, who are better treated by dietary measures. In the poorer, Coloured patients the position is different—it is usually impossible to achieve success with diets in these people.

Efficacy of metahexamide. The results of metahexamide in tolbutamide-failed cases were not impressive—nevertheless a maximum of only 300 mg. of metahexamide was used, as againste 1 - 3 g. per day of tolbutamide. Where it does work, metahexamide would appear to be more powerful, dose for dose.

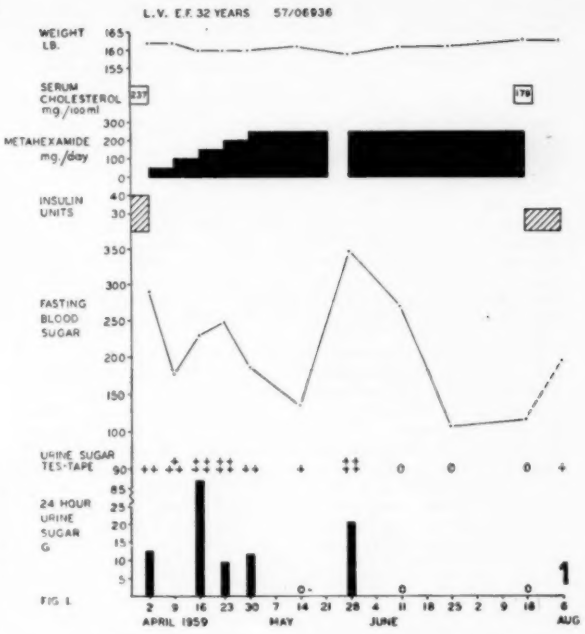


Fig. 1. This shows one of the more satisfactory responses to metahexamide. The patient was the only one in the series under 40 years of age, and had failed previously to respond adequately to tolbutamide. The high blood-sugar level with a corresponding peak in urine sugar following a period of 5 days without therapy is noteworthy.

SUMMARY

A trial of metahexamide was made in a group of diabetic patients who were believed to be suitable for oral sulphonyl-urea therapy but who had failed to respond adequately to tolbutamide. A few responded better to metahexamide but on the whole the results were disappointing. Metahexamide is no longer available.

We thank Prof. S. E. Kench and his department of Chemical Pathology for biochemical data, Dr. S. Bank for his cooperation, and the Hoechst Pharmaceutical Company. The South African Council for Scientific and Industrial Research defrayed part of the expenses through a grant to the Endocrine Research Group of the University of Cape Town.

REFERENCE

1. Jackson, W. P. U. (1958): S. Afr. Med. J., 32, 153.

MEDICAL SERVICES PLAN : PROGRESS REPORT

The Medical Services Plan accepted applications for group membership from the general public as from 1 July 1959 and thereby launched the first comprehensive, profession-sponsored, pre-paid medical care scheme on the African continent. After 6 months of operation, this report is being circulated because of numerous requests about the progress of the Plan. It is hoped that the data contained herein will bring each participating doctor up to date on the present and anticipated future developments of the Plan.

A. *Fiscal*

In order to give the Plan the initial funds necessary for establishing the scheme, it was decided to ask each participating doctor for a participation loan of £10. This loan is repayable upon the resignation or death of the doctor, or when the financial stability of the Plan warrants it. Originally, participating doctor membership was limited to the area of the Southern Transvaal Branch of the Medical Association of South Africa, but was extended to cover the doctors in the area of the East Rand Branch at the request of that Branch. From these areas 764 doctors indicated their intention of joining the Medical Services Plan as participating doctors, of whom 691 have submitted their participation loan. There are 73 still outstanding.

An amount of £1,956 12s. 7d. has been used up to September 1959 to cover costs of establishing the Plan. Included in this amount is capital expenditure for printing (stationery, envelopes, doctors' and subscribers' agreements, intention cards, applica-

tion forms, pay roll authorization deduction cards, office furniture, files, cabinets, typewriter) and salaries of the staff from February to September 1959. From October to date, the Plan has not utilized the participating doctors' loan account, but has operated off the subscribers' account and the authorized administrative deductions from approved doctors' accounts. From this short experience, barring a calamity (for example an epidemic), it is hoped that a portion of the participating doctors' loans will be repaid after a year's operation.

B. *Membership*

To date the number of subscribers in the Plan is 621, and the number of people covered is 1,628. Since one of the insurance companies has suspended taking further groups, and another has reduced the indemnity cover of its policy holders to approximate the Preferential Tariff for approved medical aid societies, the Plan has been inundated by queries from groups covered by various insurance schemes and others in regard to what the Plan's requirements are for membership.

Early in the new year the membership of the Plan can be expected to double with regard to the subscriber members and to triple as regards the number of people covered.

Although the actual area of operation of the Plan is that of the Southern Transvaal and East Rand Branches of the Medical Association of South Africa, to accommodate national groups and to obviate the injustice to a subscriber of treating as a non-participating doctor any registered medical practitioner rendering service to a subscribing member of the Plan while on business or vacation outside of the area of operation, the Board of Directors passed the following rule, which was subsequently approved by the Branch Council of the Southern Transvaal Branch and the Federal Council of the Medical Association of South Africa. The necessity for this provision will fall away as soon as the Plan is officially extended on a Union-wide basis, at which time all private practitioners in the country will have the opportunity of enrolling as participating doctors:

'*Rule I.* Where a Subscriber to the Plan or his dependant is obliged to seek medical services in an area where the Plan does not yet operate, the Plan will treat the medical practitioner concerned as a Participating Doctor for the purposes of payment, provided that the medical practitioner shall have agreed to accept payment from the Plan as a Participating Doctor before rendering services.'

In answer to numerous requests from members of the profession for personal coverage by the Plan, the Board of Directors also passed the following rule which, similarly, has received the Branch Council's and Federal Council's approval:

'*Rule II.* Subscribing Membership to Medical Services Plan is open to any registered medical practitioner. Upon acceptance of an application for membership, the medical practitioner and his dependants shall be entitled to all benefits of the Plan in accordance with the Terms and Conditions set out in the Subscriber's Contract, provided that payment shall either be made annually in advance or otherwise secured to the satisfaction of the Board of Directors of Medical Services Plan.'

It is considered that stop-order facilities will be the most convenient method of handling doctors desiring subscriber status. The Plan's stop-order forms are available on request.

C. *Experience*

The experience gained during the 6 months of operation indicates that the type of subscriber in the Plan is one who has joined primarily to protect himself and his family from the hardships of high costs of major medical, surgical and hospital services. There has been no immediate run upon the use of services, as was feared by some during the Plan's organizational stage because of the fact that the Plan offers full comprehensive coverage. The organizers were guided by the American and Canadian experience, which advised them that no such run had resulted in these countries.

On the part of the participating doctors, the Vetting Committee has had to query very few accounts.

D. *Schedule of Fees*

At the Inaugural General Meeting of the Plan it was decided that the Plan should operate on a schedule of fees equal to the medical aid tariff plus 50% or normal private practice fees, whichever were less. During the month of November, the Branch Council of the Southern Transvaal Branch of the Medical Association of South Africa instructed the Plan to adopt the schedule of fees of medical aid tariff plus 40% until such time as the Association could provide a detailed schedule of fees to be applied by the Plan.

It should be understood by participating doctors that this schedule of fees represents the maximum that the Plan will pay for services rendered. If, in treating a patient, a lesser fee would ordinarily have been charged, the Plan expects that the account will be for the lesser amount.

To expedite payment of accounts, participating doctors should instruct their receptionists to render all accounts of subscribers directly to the Plan, being sure that the subscriber's membership number, as well as the subscriber's name and address appears on the account.

All groups have been advised that their subscribers must present their membership card on seeking services, or give the doctor their membership number.

The following is a list of groups as at December 1959:

	Group No.
Medical Services Plan	1
Keatings Pharmaceuticals Ltd.	2
Denver Machinery Co. (Pty.) Ltd.	3
Westdene Products (Pty.) Ltd.	4
Cooper Brothers & Co.	5
Neon Fluorescent (S.A.) (Pty.) Ltd.	6
King David School	7
Alloy Industries	8
S.A. Blood Transfusion Service	9
National Cash Register Co. (S.A.) (Pty.) Ltd.	10
South Wales Electric (Pty.) Ltd.	11
Miodownik & Co. (Pty.) Ltd.	12
South African Milling Co. Ltd.	13
Plastic & Metal Industries (Pty.) Ltd.	14
Cyril Egnal & Co.	15
Norman Adam (Pty.) Ltd.	16
Joseph Lucas (Pty.) Ltd.	17
Bowman, Gilfillan & Blacklock	18
The Dove Insurance Corporation Ltd.	19
Direct Payments	20
E. R. Pollak Ltd.	21
Lawson Holdings (Pty.) Ltd.	22
Universal Manufacturing Engineers	23

ASSOCIATION OF PHYSICIANS OF SOUTH AFRICA (M.A.S.A)

The 'One-day' Congress organized by the Cape Western Sub-Group of this Association will now be held on Tuesday 26 January 1960 and *not* on 22 January as previously announced. The Congress will be held in the Department of Pathology of the Medical School, University of Cape Town, Observatory, Cape.

PROVISIONAL PROGRAMME

9.30 a.m. Dr. M. Nellen: Auscultation before and after open-heart surgery. (Authors: Drs. M. Nellen, V. Schrire, L. Vogelpoel and A. Swanepoel.)

10.00 a.m. Dr. M. Horwitz: Review of Reiter's syndrome and keratodermia blennorrhagicum. (Authors: Drs. J. Walker and M. Horwitz.)

10.30 a.m. Prof. A. J. Brink: Vaskulêre fistels.

11.00 a.m. Tea interval.

11.30 a.m. Dr. W. P. U. Jackson: Precocious puberty with special reference to granulosa-cell tumours.

12.00 p.m. Dr. W. F. E. Baumann: Subarachnoid haemorrhage.

12.30 p.m. Dr. T. J. Dry: Some problems in connection with the treatment of severe essential hypertension.

1.00—1.30 p.m. Lunch will be served at the Medical School.

2.00 p.m. Dr. M. Herman: Application of hypnosis in private practice with demonstrations of common phenomena in the trance state.

2.45 p.m. Dr. R. Slome: The ECG effort test.

3.15 p.m. Dr. H. A. Brown: Peptic ulceration in 'teenagers'.

3.45 p.m. Dr. I. M. Marks: Investigation of pancreatic disease.

WORLD MEDICAL ASSOCIATION

GENERAL PRACTICE RESIDENCY PROGRAM : LOUISE OBICI MEMORIAL HOSPITAL, USA

The Secretary General of the World Medical Association has again supplied the Editor of this *Journal* with brochures and application forms for those practitioners interested in the General Practice Residency Program of the Louise Obici Memorial Hospital, Suffolk, Virginia, USA. This resident training programme is offered to acceptable applicants who have completed 1 year in an approved rotating internship. The appointment is for 2 years beginning on 1 July of each year and is approved by the American Medical Association.

The first year of the course is devoted to internal medicine with clinical experience in paediatrics, psychiatry and other specialities. The second year is devoted to training in general surgery, obstetrics, gynaecology, radiology and clinical pathology. The resident is expected to take part in conferences and rounds conducted by faculty members of the Medical College of Virginia, and will have a rotated assignment in the emergency room of the hospital.

The Louise Obici Memorial Hospital has a staff of 59 physicians and dentists, with a capacity of 138 adult beds and 32 bassinets.

Graduates of foreign medical schools desiring appointment must receive certification from the Educational Council of Foreign Medical Graduates. Inquiries on the procedure to obtain certification should be addressed to the Council at their headquarters, 1710 Orrington Avenue, Evanston, Illinois, USA.

The appointment carries a salary of $3,000 per year and complete maintenance. Furnished quarters are available for married doctors and their families, the rent being paid by the hospital and the resident defraying the cost of utilities.

Application forms and a limited number of brochures are available on application to the Editor of this *Journal* at P.O. Box 643, Cape Town, but further information may also be obtained from the Chairman, Resident Training Committee, Louise Obici Memorial Hospital, Suffolk, Virginia, USA.

IN DIE VERBYGAAN : PASSING EVENTS

Members are reminded that they should notify any change of address to the Secretary of the Medical Association of South Africa at P.O. Box 643, Cape Town, as well as to the Registrar of the South African Medical and Dental Council, P.O. Box 205, Pretoria. Failure to advise the Association will result in non-delivery of the *Journal*. This applies to members proceeding overseas as well as to those who change their addresses within the Union.

* * *

Universiteit van Stellenbosch. Die Departement Interne Geneeskunde van die Fakulteit van Geneeskunde, Karl Bremer-Hospitaal, Bellville, Kaap, hou weekliks 'n kliniese personeelbyeenkoms wanneer besprekings oor pasiënte gevoer word. Aangesien daar al heelwat navrae deur algemene praktisyns was oor die moontlikheid of hulle ook dié byeenkomste kan bywoon, het die Departement besluit om die byeenkomste vir algemene praktisyns oop te stel en om hulle uit te nooi om daaraan deel te neem. Die byeenkomste word op Saterdae om 9 vm. in die groot lesingsaal by die Karl Bremer-Hospitaal gehou, en 'n aanvang daarmee sal weer op 6 Februarie 1960 gemaak word.

NUWE PREPARATE EN TOESTELLE : NEW PREPARATIONS AND APPLIANCES

PARABAL

Westdene Products (Pty.) Ltd. announce the introduction of Parabal, the detoxicated form of phenobarbitone discovered in the research laboratories of the West Pharmaceutical Co. Ltd. of England, and supply the following information:

Parabal enables the dosage of phenobarbitone to be reduced by 80% without loss of sedation. This striking result is achieved by combining phenobarbitone with an amino-acid derivative. Absorption of the new presentation is much more rapid than that of phenobarbitone itself and the excretion rate is far greater. As a result, the advantages of phenobarbitone therapy are maintained but the side-effects such as 'hangover' and 'dopiness' are eliminated.

Parabal is indicated in the treatment of psychosomatic disorders, personality upsets characterized by marked anxiety or nervous tension, hypertension, simple insomnia, intensive and neurotic symptoms associated with the menopause, etc. In addition, trials being carried out in Johannesburg indicate that Parabal has a definite place in the treatment of epilepsy.

The average dosage for Parabal is 1 tablet night and morning for adults and this may be increased if necessary to 2 tablets 3 times a day. Parabal may be administered with safety to children, the usual dosage being ¼ - ½ tablet according to age. This low dosage emphasizes a further advantage of Parabal which is its low cost compared with other sedative drugs.

Parabal is available in bottles of 100 and 500 tablets.

Further information may be obtained from the sole South African distributors, Westdene Products (Pty.) Ltd., P.O. Box 7710, Johannesburg.

CALPOL

Westdene Products (Pty.) Ltd. announce the introduction of Calpol (paracetamol), manufactured by Calmic Limited of England, and supply the following information:

Calpol is offered as a safe alternative to aspirin medication. It has an analgesic action slightly greater than that of aspirin, but has no irritant action on the gastric mucosa. It may therefore be prescribed without the risk of causing the occult submucosal bleeding which may be associated with prolonged administration of acetylsalicylic acid.[1] In chronic rheumatic disorders Hamilton[2] has shown that paracetamol has an analgesic value equal to that of compound codeine and has fewer side-effects. Its antipyretic effect is equal to that of aspirin and is more rapid in onset though not quite to long-lasting.[3]

Calpol is indicated for the relief of rheumatic pain, neuralgia, dysmenorrhoea, headaches, coryza, tonsillitis and other pyrexial conditions. It is a particularly safe and effective antipyretic for children.[4] Pain arising from smooth muscle spasm in hollow viscera is not alleviated and paracetamol, unlike acetylsalicylic acid is not effective in acute rheumatic fever or polyarthritis.

Dosage. Adults: 1 - 2 tablets 3 times daily; children (2 - 6 years of age): ¼ - ½ tablet; and children (7 - 12 years of age): ½ - 1 tablet.

Calpol is available in bottles of 50, 100 and 500 tablets.

Further information regarding Calpol may be obtained from the sole South African distributors, Westdene Products (Pty.) Ltd., P.O. Box 7710, Johannesburg.

1. Editorial (1959): Brit. Med. J., 1, 349.
2. Hamilton, R. R. (1956): Lancet, 1, 322.
3. Boschill, A. B., Nach, C. B. and Wheeler, A. G. (1958): J. Amer. Pharm. Assoc., 47, 479.
4. Correly, D. A. and Ritter, J. A. (1956): J. Amer. Med. Assoc., 160, 1219.

BOEKBESPREKINGS : BOOK REVIEWS

BLAASKARSINOOM

Neoplastic Disease at Various Sites. Algemene Redakteur: D. W. Smithers, M.D., F.R.C.P., F.F.R. Deel II. *Tumours of the Bladder.* Geredigeer deur David M. Wallace, O.B.E., M.S., F.R.C.S. Pp. xvi + 352. 202 afbeeldings. 60s. net + 2s. 8d. posgeld oorsee. Edinburgh en Londen: E. & S. Livingstone Bpk. 1959.

Die behandeling van blaaskarsinoom bly nog steeds een van die grootste probleme vir 'n uroloog. Die skrywers van hierdie boek moet gelukgewens word met die wyse waarop die probleem uiteengesit word.

Die deel oor die moontlike etiologie van blaas-tumore in die industrieë sowel as in die algemene bevolking word baie breedvoerig bespreek met die allernuutste eksperimentele gegewens daaroor. Die patologiese en kliniese patologie van blaas-tumore word in 'n baie praktiese lig benader, en behoort van besondere waarde te wees by die kliniese klassifikasie van blaas-tumore en dus ook die gewenste behandeling.

Metodes van chirurgiese behandeling, radioterapeutiese behandeling (insluitende radio-isotope sowel as supervolt-behandeling) is baie volledig opgestel, en 'n besonder eerlike houding word ingeneem oor die sukses van elke behandeling.

Die oorsig van metodes van behandeling en die resultate verkry in die Royal Marsden-, St. Peters-, St. Phillips- en St. Pauls-Hospitale word vergelyk met vorige publikasies.

Die boek is uniek en sal dus van baie waarde wees vir die uroloë en patoloë wat geïnteresseerd is in blaastumore. T.C.H.A.

DIE BEHANDELING VAN KANKER

Treatment of Cancer and Allied Diseases. 2e uitgawe. Deel 2. *Tumors of the Nervous System.* Deur 30 skrywers, geredigeer deur Georg T. Pack, M.D., F.A.C.S. en Irving M. Ariel, M.D., F.A.C.S. Pp. xvii + 316. 340 illustrasies. $15.00. New York: Paul B. Hoeber, Inc. 1959.

Hierdie bundel behandel maligne toestande van die sentrale senuweestelsel. Omtrent driekwart van die inhoud is bestee aan diagnose, radioterapie en chirurgiese behandeling van breingewasse. Al die mees moderne metodes in verband met diagnose, soos röntgenografie, ventrikulografie, ensefalografie, elektroensefalografie, miëlografie, angiografie asook die gebruik van radio-aktiewe isotope vir diagnostiese doeleindes, word breedvoerig in hierdie bundel bespreek.

Die paar hoofstukke oor die chirurgiese tegnieke wat by hierdie toestande toegepas word, is pragtig duidelik met goeie afbeeldings geïllustreer. Spesiale hoofstukke geskrywe deur vooraanstaande neurochirurge oor gliomata, hipofese-gewasse en meningiomata maak die kern uit van die deel oor die brein self.

Daar is ook pragtige hoofstukke oor tumore van die perifere senuweestelsel, sowel as van die simpatiese ganglia en paraganglioniese selle.

Die bundel sluit af met 'n hoofstuk wat handel oor chirurgiese metodes vir pynverligting soos by baie van die pasiënte gesien word.

Dit is dus uit alle oogpunte beskou 'n uitstekende naslaanboek vir die neurochirurg, sowel as vir die algemene chirurg en die nagraadse student. J.J.D.J.

VERSORGING VOOR EN NA DIE OPERASIE

Illustrated Preoperative and Postoperative Care. Deur Philip Thorek, M.D., F.A.C.S., F.I.C.S. Pp. xi + 98. 60 illustrasies. 30s. net. Londen: Pitman Mediese Uitgewers Kie. Bpk. 1959.

Wat 'n pragtige klein boekie! Iedere prentjie vertel 'n storie. Só mooi afgebeeld is iedere prentjie, en só prakties gekies, dat die verduidelikings amper oorbodig lyk. Elke huisdokter, kliniese-assistent en selfs die chirurg kan maar intelligent deur die boekie blaai—veral in hierdie tyd wanneer iedereen dink dat die data van die laboratorium die laaste antwoord op alle vrae bied.

Die meeste tekens wat belangrik is by die opsomming van die pasiënt se toestand voor die operasie, tot al die gewone probleme wat van tyd tot tyd na die operasie verskyn, is hier opgeteken en só gestel dat 'n mens dit met een oogopslag kan raaksien. J.J.D.J.

INNERVATION OF MUSCLE STUDIED BY BIOPSY

The Innervation of Muscle. A biopsy study. By. C. Coërs and A. L. Woolf, M.D. Pp. xv + 149. 281 figures. 42s. Oxford: Blackwell Scientific Publications. 1959.

This valuable monograph describes in detail the techniques of muscle biopsy and of histological preparation of the biopsy material which the authors have found most effective for demonstrating nerve-endings in muscle. Emphasis is laid on the localization of motor end-plates to particular regions of each type of muscle and the method of determining the correct site for biopsy is described. The normal structure of the motor end-plate of various species is described in detail, and also the several types of nerve ending found in the muscle spindle. Stress is laid on the ratio of motor end-plates to terminal axons and it is shown how this ratio is increased in many degenerative diseases. The histological appearance of motor end-plates and of axons is found to be of diagnostic and prognostic significance in a wide range of diseases of nerve and of muscle including such diverse conditions as anterior poliomyelitis, peripheral neuritis, and the myopathies. Histological appearances are correlated with clinical and electromyographic observations on many of the cases described.

The book is excellently produced and lavishly illustrated with photomicrographs of high quality. Not only are the theoretical considerations of the greatest interest to physiologists, pathologists and neurologists, but practical instructions are sufficiently explicit to enable the research worker to apply the same techniques to his own investigations. Authors and publisher are to be congratulated on an important contribution to medical literature. A.W.S.

BRIEWERUBRIEK : CORRESPONDENCE

REGISTRATION OF OPTOMETRISTS

To the Editor: I am very grateful to Dr. Struthers for taking the trouble to reply[1] to my letter,[2] published in the *Journal* of 28 November 1959. I am sure that both he and you, sir, have no desire to start a prolonged verbal tussle over my letter, but there are certain points made by him which may convey a wrong impression to the medical profession, and I should be pleased to use your columns to correct these.

The Ophthalmological Society is not against the principle that all supplementary health services should be under the control of the Medical Council, and is in favour of such control for optometric services. It is the details of the control that have caused such disappointment among my colleagues. Federal Council was quite prepared to give optometrists a status which they have never deserved. From an academic standpoint, to establish a learned profession by legislative enactment rather than by educational evolution, is totally untenable.

Dr. Struthers mentions that when the *ad hoc* committee met, the President of the Ophthalmological Society considered that all cases requiring orthoptic treatment must first be referred to an ophthalmic surgeon, rather than to a medical practitioner. 'It was not considered that the family doctor was qualified to advise his patient adequately as to what was in his best interest'. This statement is a distortion of the truth, and can only be construed as a means to enlist the support of the general practitioners. The President actually insisted that if an optician practised orthoptic treatment, he should at least be adequately trained for it. We are well aware that the opticians have a nodding acquaintance with orthoptics, but there is a group of well-trained orthoptists who are registered with Medical Council in whom the ophthalmologists have every confidence. The *ad hoc* committee was considering having two classes of orthoptists, one working under medical supervision, hospital trained, and possessing a diploma which ensures the patient adequate safeguards; and the other for opticians having direct access to the public, a training which does not include hospital patients and which the foremost authority in the world, Keith Lyle, regards as superficial. Surely before these persons are allowed to treat the public, the family doctor should be aware of their limitations, and if he is not aware of them the case should be seen by an ophthalmologist, who could adequately advise the patient what was in his best interest?

Laws are not made for the protection of experts, but for the public—that vast multitude which includes the ignorant, the unthinking and the credulous. That is also the democratic way.

It would be interesting to hear from Federal Councillors what made them decide to vote the way they did.

Anti-lechis

Johannesburg
18 December 1959

1. Correspondence (1959): S. Afr. Med. J., 33, 1025.
2. *Idem* (1959): *Ibid.*, 33, 1026.

MEDICAL AID SOCIETIES AND MEDICAL INSURANCE SCHEMES

To the Editor: It is with a great deal of interest that I have recently read certain documents dealing with medical aid societies and medical insurance schemes.

Firstly, the Association's memorandum, 'An explanation as to the difference', is an excellent and timely explanation, but I feel the final paragraph carries a sting which might well have been omitted. A factual document did not require this expression of opinion, particularly from an employee of the Association.

Secondly, there was an excellent article in the December issue of *The Financial Times*. The minor errors in nomenclature do not cloud this good attempt to give a clear and concise picture of the present-day position. I quote: 'Many actuaries have long contended that the South African Mutual Life Assurance Co. and SANLAM started their schemes with premiums which were fixed at too low a figure'. Are we to subsidize commercial companies because of their actuarial errors?

Further quotations read: 'The long-established private medical aid societies are extremely worried about the effect of any concession on their 200 organizations. Already 10 societies have gone under or have been forced to amalgamate, and others have been adversely affected by the impact of the big scale organizations of the commercial companies. If the full preferential tariff were granted to commercial schemes, the existence of the medical aid societies would be gravely threatened'. 'The profession-sponsored Medical Services Plan does not seek the Preferential Tariff since its schedule of fees is based upon normal private practice fees. By policy, therefore, doctors treating patients covered by insurance companies or the Medical Services Plan should charge normal private practice fees'.

Our Association has fostered the principles of the non-profit making medical aid society to the benefit of the patient and doctors, and it is now well known that there are methods of negotiation intended to resolve amicably differences between the societies and the Association when such difficulties arise. Why should 'our' medical aid societies and Association be subject to such a threat as is implied in this article, and our own Medical Services Plan be jeopardized before it can prove itself?

The third document is SANSOM's circular to members. It came into my hands in these circumstances: Certain services were rendered to a patient. I decided the patient's position was such that I should render my fee at tariff book rates. This amounted to £5 10s. 0d. SANSOM sent me a cheque for £4 13s. 0d., a reduction of 16%, *via* the patient, who sent me all the correspondence. The circular imputed that I charged more than the preferential tariff, which in this case I did not because in my opinion the patient would have been unduly embarrassed had I charged full private fees, especially as my services were likely to be required in this disease on numerous occasions.

SANSOM's document reads as follows: 'We have pleasure in forwarding herewith our cheque for the accompanying claim. The cheque has been made out in favour of your doctor/hospital and we should be pleased if you would hand the cheque to your doctor/hospital.

'The benefits allowed herewith represent 100% of the fees according to the Preferential Tariff dated January 1959, i.e. the specially reduced tariff at present allowed to members of approved sick funds by doctors and specialists. Since our medical aid schemes provide a valuable service to the medical profession, it is reasonable that reduced fees according to the Preferential Tariff should be applied as is already done by many doctors.

'If your doctor is not prepared to allow the reduced fee according to the Preferential Tariff in your case, we shall consider a further payment, but it will first be necessary for you to pay the balance of the doctor's account yourself and to forward the receipt to us together with the doctor's receipt in respect of the attached cheque as well as the attached detailed accounts.

'We would mention that you are entitled to 80% of medical expenses and 100% of operation expenses only. Your own contribution to this claim is included in the amount of the attached cheque. If the reduced fees according to the Preferential Tariff is applied, you need not refund your own contribution to us, but we would point out that we may in future decide to collect members' own contributions to further claims if we should find that this is necessitated by our claims experience.

'If your doctor does not apply the Preferential Tariff, your own contribution to the claim will be larger and you will be responsible for the full amount of your own contribution.'

I have quoted it in full because its contents have been rumoured a great deal recently, and I have been expecting the Editor to publish it in the *South African Medical Journal*. I cannot understand why he has not, as its subject matter and implications are tremendously important to all members of the profession.

So far I have only been critical and obviously against any agreements with commercial insurance companies. May I now be a little constructive?

As a profession we should learn from our legal *confrères*. Let the South African Medical and Dental Council lay down a *minimum* tariff, which might well be the Preferential Tariff as in the Tariff Book applicable to medical aid societies.

While permitting a practitioner to treat any patient *pro deo*, to charge less than the minimum would be an act of undercutting and subject to disciplinary action by the Medical Council. Let us also reserve the right to charge any higher sum, provided we can, if requested, justify such charge.

The medical aid societies, we ourselves, the patients, and the Medical Services Plan would thus be protected, and commercial insurance companies would have to calculate their premiums according to experience and information which is available to any one.

M. J. G. Davies

102 Lister Buildings
Jeppe Street, Johannesburg
18 December 1959

[It is necessary to point out to our correspondent that the Secretary, in formulating the circular letter which was sent to every member of the Association, did not indulge in an irresponsible expression of his own opinion, but carried out the wishes of Federal Council. It is also regrettably necessary to advise our correspondent to ponder the fact that the Secretary of the Association is a responsible senior colleague and not merely an employee.

The role of the medical aid societies and the medical insurance schemes has been discussed freely and fully in our correspondence columns. In view of the fact that opinions still differ radically on this subject and that the comprehensive letter dealing with the matter was sent to every member of the Association, no further editorial action was indicated at this stage—Editor.]

MEDICAL AID SOCIETIES AND MEDICAL INSURANCE SCHEMES

To the Editor: As Chairman of the Central Committee for Contract Practice, my Committee and I conducted negotiations with the Advisory Council of Medical Aid Societies on numerous occasions. At all times I found them reasonable, intelligent people, as long as they were not subjected to soapbox oratory.

I feel it is my duty to enlighten many of my colleagues on certain facts of which so many of them seem totally unaware.

Medical aid societies cater for a low income group. The average basic income of 75% of their members is under £600 a year. Only 0·82% earn over £2,500 a year. Most of these people would have been treated as free patients in Provincial hospitals if they did not belong to medical aid societies.

A certain type of practitioner makes a terrific fuss if he encounters the odd member earning more than £2,500 a year. He forgets that for each one of these, he has been paid perhaps for 50 others, who normally would have been hospital patients.

Medical aid fees are acceptable to the vast majority of medical practitioners and specialists, in spite of vigorous propaganda by a vociferous minority—the most garrulous since the time of Hippocrates!

Medical aid societies pay the general practitioner in Johannesburg 20s. a visit, and there are no bad debts. Over-visiting has been the bane of medical aid societies. In numerous places in the Union medical aid fees are, in actual fact, private fees.

In 1948, when the Association was at loggerheads with the Transvaal Provincial Administration, the Central Committee for Contract Practice met the Advisory Council of Medical Aid Societies. They clearly indicated that they wanted their members to be attended in hospital by medical practitioners of their own

choice and were prepared to pay for this privilege. They approved of our stand against the Hospital Ordinance as envisaged by them.

In 1950 the Federal Council of the Medical Association passed an unanimous resolution that the formation of medical aid societies should be encouraged.

We were scared of a State Medical Scheme and welcomed the support of the Advisory Council. We all know that our quarrel with the Provincial Administration was settled satisfactorily. No sooner was the danger past than certain vociferous Federal Council members turned against our former allies, the Advisory Council of Medical Aid Societies. Such disloyalty one would never have expected from our colleagues.

The medical aid societies are rendering excellent service and mean approximately 1½ million pounds to the profession every year, from a low income group which would otherwise have been hospital cases.

Medical Services Plan

We all welcomed this Plan. I was on the Committee of the Plan until the meeting of Federal Council in April 1957 at Vereeniging when, for reasons of my own, I resigned. I duly sent my cheque and became a participating member from the Plan's inception. When the Plan was discussed in Federal Council afterwards I studiously avoided expressing any opinion.

The Medical Services Plan, which caters for all income groups and which is to be the model for all other societies, offers general practitioners a *maximum* of 22s. 6d. for a domiciliary visit and for specialists the *maximum* medical aid fees plus 40%, less 10% of the total amount for collection fees.

Pro-ration, which means accepting a proportion of the fees if the finances are inadequate, has been introduced. This is something revolutionary and may have far-reaching implications and repercussions. Medical aid societies are forced to pay 100% even if their finances are in dire straits. If not, recognition is withdrawn.

Under these circumstances how can anyone legitimately have a complaint against the tariff of fees laid down for medical aid societies?

Insurance Schemes

These schemes cover individuals and groups of people, the vast majority of whom belong to the same income group as members of the medical aid societies.

The Central Committee for Contract Practice met representatives of the Mutual Medical Aid Society of 1954 on two occasions. Mr. Human was the Secretary then and there were 2 medical practitioners on their Board. On the last occasion they requested us to lay down our fees and they would pay them. They also offered to allow the Medical Association of South Africa to nominate 4 more members on their Board. What could be fairer? This was not accepted by Federal Council. The Central Committee for Contract Practice twice recommended that they be recognized, but Federal Council rejected this because they accepted members earning over £2,500 a year.

In November 1958 the Executive Committee (Transvaal members) of the Central Committee for Contract Practice met representatives of SANSOM and the Mutual Medical Aid Society. The Executive Committee was a fact-finding Committee and had no mandate to make a recommendation. I was very much impressed with what the representatives said of these societies. SANSOM offered to pay medical aid rates plus 33⅓% and the Mutual Medical Aid Society plus 25%. No maximum was laid down for people in the higher income group as is laid down by the Medical Services Plan, which is to be the model for all other plans. After all, who knows better than the attending doctor, which patients belong to the higher income group and which do not.

If a medical practitioner charged a higher fee than the plus 33⅓% and plus 25%, he would have been allowed to collect the difference between these amounts and his private fee himself. There was in actual fact no limitation of fees.

Federal Council did not grant recognition to these insurance companies. A big factor in this refusal was the desire to give the Medical Services Plan every opportunity to make good, and the following statement was made by the Chairman of the Board of the Medical Services Plan: 'Give recognition to the insurance schemes and the Medical Services Plan will cease operations immediately.'

Criticism of the Central Committee for Contract Practice

When the new tariff of fees was negotiated with the Advisory Council of Medical Aid Societies, it received general approval, with the exception of a few vociferous medical practitioners north of the Vaal.

A Committee to investigate the economics of general practice was appointed by the Southern Transvaal Branch Council under the chairmanship of a specialist. In a memorandum, he later suggested that the visiting fee for a general practitioner should be 41s., or some such ridiculous figure.

In October 1958 a delegation from the Southern Transvaal Branch of the National General Practitioners Group was received by Federal Council in Pretoria. The data supplied by the delegation was not very accurate, and they were rather confused. They suggested a visiting fee for general practitioners of 31s. 6d. for medical aid societies, while admitting that it was higher than the private fee. Where the preferential rate comes in, Heaven alone knows!

This deputation severely criticized the Central Committee for Contract Practice for having let the general practitioners down. They hoodwinked themselves into thinking that under the Medical Services Plan they would receive a very high fee for visits. They were disillusioned because the Committee of the Medical Services Plan decided, very wisely, on a much lower fee than the 31s. 6d. they were expecting.

Although most of the critics of the Central Committee for Contract Practice are subscribers to the Medical Services Plan, they have not raised their voices in protest against a fee which they thought was totally inadequate in October 1958. Have they perhaps now adopted a more reasonable attitude and recognized that no medical aid society or insurance company can possibly pay 31s. 6d. for a day visit? Medical practitioners would be well advised not to pay any attention to agitators in the profession who have no time for any medical aid society or benefit society.

Revision of Tariff

The Tariff of Fees for Medical Aid Societies is due to be revised during 1960. It is to be hoped that Groups will not make unreasonable demands on the medical aid societies, most of which are already in the red. It is quite likely, not without reason, that the Advisory Council of Medical Aid Societies may request a reduction of certain fees.

There is no reason why the Medical Services Plan, medical aid societies, and insurance schemes should not all function concurrently. The more cover that is provided for the public in pre-paid medical aid schemes, the better.

After all, a serious illness in a middle-income-group family can cause a financial calamity. We must remember that we make our living out of the misfortunes of our fellow citizens, and we must at all times be reasonable with them as well as fair to ourselves.

The purpose of this letter is to give my colleagues the true facts and request them to have faith in the Central Committee for Contract Practice, who negotiate on their behalf and who have the facts and knowledge available and are in the best position to judge what is in the best interest of the profession and the public.

The Central Committee for Contract Practice consists of members from all the big centres in the Union. They are supposed to have a specialized knowledge of medical aid society matters. They have never let the profession down and Federal Council must approve of all their actions. It is an impartial body and is there to protect both the public and the profession from exploitation. Criticism is often based on lack of knowledge of the true facts of the position.

I regretted very much having had to resign from the Chairmanship of the Central Committee for Contract Practice and from Federal Council when I was elected to the South African Medical and Dental Council in 1958. I do not have the time to serve on Federal Council and on the Medical Council as well.

I sincerely trust that the good relationship between the Central Committee for Contract Practice and the Advisory Council of Medical Aid Societies and insurance companies will continue.

L. O. Vercueil

106 Conrad Street
Florida, Transvaal
8 December 1959